
# TASIMELTEON

# ADVISORY COMMITTEE MEETING BRIEFING MATERIALS

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ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

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| **Abbreviation** | **Description** |
|---|---|
| ACTH | Adrenocorticotropic Hormone |
| ADME | Absorption, Distribution, Metabolism, and Excretion |
| AE | Adverse Event |
| ALL | Acute Lymphocytic Leukemia |
| AME | Absorption, Metabolism, and Excretion |
| aMT6s | Primary metabolite of melatonin |
| ANCOVA | Analysis of Covariance |
| ANOVA | Analysis of Variance |
| AUC | Area Under the Plasma Concentration-Time Curve |
| BMI | Body Mass Index |
| BMS | Bristol-Myers Squibb |
| BWSQ | Benzodiazepine Withdrawal Symptom Questionnaire |
| $^{14}C$ | Carbon-14 |
| $C_{max}$ | Maximum Observed Plasma Concentration |
| CGI-C | Clinical Global Impression of Change |
| CI | Confidence Interval |
| CLcr | Creatinine clearance |
| CL/F | Clearance/ Fraction Absorbed |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| CTS | Circadian Timing System |
| CYP | Cytochrome |
| DDI | Drug-drug interaction |
| DLMO | Dim Light Melatonin Onset |
| DMRA | Dual melatonin receptor agonist |
| DSST | Digit Symbol Substitution Test |
| ECG | Electrocardiogram |
| eGFR | Estimated Glomerular Filtration Rate |
| FDA | Food and Drug Administration |
| FSH | Follicle Stimulating Hormone |
| g/kg | Gram/ Kilogram |
| GABA | Gamma-Aminobutyric Acid |
| h | Hour |
| HV | Healthy Volunteers |
| ICSD | International Classification of Sleep Disorders |
| $IC_{50}$ | Half Maximal Inhibitory Concentration |
| IME | Important Medical Event |
| ipRGC | intrinsically photosensitive Retinal Ganglion Cells |
| i.v. | intravenous |
| ITT | Intent to Treat |
| IVRS | Interactive Voice Recording System |
| kg | Kilogram |
| $K_i$ | Absolute Inhibition Constant |
| L | Liter |

| | |
|---|---|
| LH | Luteinizing Hormone |
| LPS | Latency to Persistent Sleep |
| LQ-nTST | Lower Quartile of Subject Nighttime Total Sleep Time |
| LS | Least-Squares |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligram |
| min | Minute |
| mL | Milliliter |
| MoST | Midpoint of Sleep Timing |
| $MT_1$ | Melatonin Receptor, Type 1 |
| $MT_2$ | Melatonin Receptor, Type 2 |
| N24CRS | Non-24 Clinical Response Scale |
| NDA | New Drug Application |
| ng | Nanogram |
| nM | Nanomolar |
| NMDA | N-methyl-D-aspartate |
| Non-24 | Non-24-Hour Disorder |
| OL | Open Label |
| OLE | Open Label Extension |
| PBO | Placebo |
| PD | Pharmacodynamic |
| PK | Pharmacokinetic |
| POC | Proof of Concept |
| PT | Preferred Term |
| QD | Once Daily |
| QT | QT Interval; the time period between the beginning of the Q wave to the end of the T wave, expressed in milliseconds |
| QTcI | QT Interval Individually Corrected |
| REM | Rapid Eye Movement |
| RESET | **R**andomized withdrawal study of the **E**fficacy and **S**afety of **T**asimelteon (VP-VEC-162-3203) |
| RHT | Retinohypothalmic Tract |
| SAE | Serious Adverse Event |
| SAS | Statistical Analysis Software |
| SCN | Suprachiasmatic Nucleus |
| SD | Standard Deviation |
| SET | **S**afety and **E**fficacy of **T**asimelteon (VP-VEC-162-3201) |
| SOC | System Organ Class |
| $\tau$ | Circadian Period (tau) |
| TEAE | Treatment-emergent adverse event |
| T3 | Triiodothyronine |
| T4 | Total Thyroxine |
| $T_{max}$ | Median Peak Concentration |
| dTSD | Daytime Total Sleep Duration |
| TSH | Thyroid Stimulating Hormone |
| nTST | Nighttime Total Sleep Time |
| $T_{1/2}$ | Terminal Plasma Elimination Half-Life |
| UQ-dTSD | Upper Quartile of Daytime Total Sleep Duration |

| | |
|---|---|
| µCi | Micro curie |
| US | United States of America |
| VAS | Visual Analog Scale |
| WASO | Wake After Sleep Onset |
| WSQ | Weekly Sleep Questionnaire |
| y.o. | Years Old |

# 1. EXECUTIVE SUMMARY

## Tasimelteon is a novel Circadian Regulator for the treatment of Non-24-Hour Disorder (Non-24) in the totally blind

Tasimelteon is proposed for the indication of the treatment of Non-24-Hour Disorder in the totally blind due to its ability to address both the underlying mechanism of the disease as well as the clinical expression of the disorder. Tasimelteon is proposed to be the first member of an Established Pharmacologic Class of Circadian Regulators because of its ability to entrain (synchronize) the Master clock to a 24-hour day and as a result align the circadian rhythms of hormones and physiological functions to a 24-hour clock.

## Non-24 is a rare, orphan, serious, chronic debilitating disorder for which there is no available treatment

Non-24 was first described in 1948 by Remler in Germany in blind individuals, and while the disorder is rare in the general population, it is highly prevalent among the totally blind. More than half of the totally blind individuals are expected to suffer from Non-24. It is estimated that approximately 80,000 people have the disorder in the United States (US).

Tasimelteon has been designated as an orphan drug by the US Food and Drug Administration (FDA) for the treatment of Non-24 in the totally blind. Non-24 is a serious disorder that impacts significantly the daily function of patients. Blind patients with the disorder struggle throughout their lives to synchronize their sleep and wake schedules with the demands of a 24-hour society. They often find themselves unable to participate in the scheduled activities of school, work and social functions. As a result blind patients with Non-24 have a diminished opportunity of fully participating in the sighted 24-hour society. While the chief complaint is usually related to the sleep-wake pattern, current research recognizes that the desynchrony of circadian rhythms, which include those of cortisol, core temperature, blood pressure, glucose control, have profound impacts in the cardiovascular and metabolic homeostasis of the body.

There is currently no available treatment for Non-24. Awareness of the disorder is low among patients and health care providers and Non-24 is often misdiagnosed as insomnia, major depression, or even dementia, further complicating the treatment paradigm.

## Non-24 is caused by the inability to perceive light through the retina and reset the circadian Master Clock in the Suprachiasmatic Nucleus (SCN)

The suprachiasmatic nucleus (SCN) is a small group of about 20,000 neurons in the hypothalamus tasked with controlling the circadian (daily) rhythms of the body. The SCN has its internal rhythm, which in the majority of people is greater than 24.0 hours and in blind people has an average period of about 24.5 hours. For example, this means that if left alone the SCN internal rhythm will be in alignment with the 24-hour clock once every 48 days. However, the SCN is reset daily back to a 24.0 hour period through the perception of light in sighted individuals. Light perceived through the retina, is transmitted through the retinohypothalamic tract to the SCN resetting the 24.5 hour period back to a 24.0 hour period on a daily basis. Blind people who cannot perceive light are unable to reset the SCN neurons and as a result they experience Non-24-Hour Disorder, a serious disorder of inability to "entrain" the SCN to a 24-hour day.

As a result of this lack of entrainment of the SCN, the circadian rhythms of patients with Non-24 are governed by their internal Master clock rhythm. Given that the average internal circadian period ($\tau$) is about 24.5 hours in the totally blind, the circadian rhythms of patients with Non-24 are progressively delayed by a half hour every day. If the internal timing of sleep propensity on Day 1 was at 10 pm, this progressive delay will result on Day 24 to shift the timing of sleep propensity to 10 am, leading to a complete inversion of the sleep-wake pattern. This progression is non-remitting and its cyclical nature brings into alignment the patient with the 24-hour day briefly every 48 or so days as it cycles in and out of phase.

## Entrainment of the Master Clock is universally accepted as the goal of therapy for Non-24

In Non-24 the SCN is not reset by light and as a result it continues to oscillate with an internal period greater than 24. The synchronization of the SCN period to a 24-hour day is referred to as Entrainment and therefore the definitional marker for Non-24-Hour Disorder is absence of entrainment. Well established methods allow for the precise measurement of the circadian period ($\tau$) and as result the determination whether a patient exhibits a period of 24.0 hours or not. A demonstration of a period ($\tau$) equal to 24.0 hours is defined as entrainment. Patients with Non-24 are by definition not entrained. The goal of a specific therapy that addresses the underlying pathophysiology of the disorder, is the achievement of entrainment in otherwise not entrained Non-24 patients. Circadian period, $\tau$, has historically been measured by either body temperature, cortisol or melatonin. Melatonin peaks at night, while cortisol peaks in the morning. They are both regulated by the Master clock at the SCN and their circadian periods match that of the SCN. Melatonin is the preferred method for measuring circadian period as it is not masked by other factors except light which suppresses melatonin.

## Sleep -wake patterns and daily functioning can be severely affected in patients with Non-24, although the pattern of disruption varies from patient to patient

Lack of entrainment of the SCN also results in lack of entrainment of the circadian sleep-wake cycle. Patients with Non-24 struggle to maintain a sleep-wake schedule compatible with the external 24-hour clock. As a result, patients with Non-24 often have disrupted sleep-wake patterns, expressed by the inability to consolidate their nighttime sleep into one episode and strong circadian drives to sleep during the daytime. It is important to recognize that the patterns of disruption vary from individual to individual based on social constraints and their tolerance of the struggle to force themselves to sleep at night and stay awake during the day in violation of their circadian cycles. There are a few patients who allow their internal rhythm to take over, while, most resist. As a result it is only a small fraction of patients that experience a daily delay of their initiation of sleep followed by a period of consolidated sleep albeit at the wrong time of the day. The majority of patients try to sleep at night and try to stay awake during the day and as a result the pattern of the sleep-wake disruption is that of a cyclical disruption of consolidation of sleep at night, often accompanied by daytime sleep episodes especially at those times when their internal circadian rhythm is completely out of phase with the 24-hour day. On average when out of phase Non-24 patients may sleep as little as 3 hours a day and experience daytime sleep episodes of 2 hours or more (Table 8). This severe impairment of the sleep-wake cycle is incompatible with the normal activities of school, work and relationships and result in impaired functioning including decreased alertness and concentration leading to a lifelong disability.

## The clinical program of tasimelteon in Non-24 included two pivotal studies with prospectively defined endpoints of Entrainment and Clinical Response

The two pivotal Phase III studies, Safety and Efficacy of Tasimelteon (SET:84 patients) and the Randomized Withdrawal study of the Safety and Efficacy of Tasimelteon (RESET:20 patients) assessed the efficacy and safety of tasimelteon in Non-24 patients.

Eighty-four patients participated in the SET study. These patients had an average $\tau = 24.47$ hours, an average sleep amount in the worst 25% of nights of 3.25 hours per night and an average daytime sleep episode of 2.41 hours per day in the worst 25% of days. Tasimelteon succeeded in entraining the Master clock, in 20% (8/40) of the patients as early as the first month of treatment and in 59% by month 7 (10/17). Tasimelteon-treated patients also experienced significant improvements in clinical measures of the sleep and wake cycle, and functionality. These improvements were seen both in the composite Non-24 Clinical Response Scale (N24CRS) as well as on each individual component of the scale; nighttime sleep (LQ-nTST), daytime sleep (UQ-dTSD), midpoint of sleep (MoST) and global functioning (CGI-C). During the worst 25% of nights, tasimelteon treated patients sleep improved by about 57 minutes per night, and daytime sleep was reduced by 46 minutes per day. In addition over the 6 month observation period, in the majority of responders (entrained on tasimelteon), the overall global functioning of patients was rated as “much improved” or “very much improved”.

In the RESET study 20 patients who had received tasimelteon for 12 weeks and had become entrained were randomized to drug or placebo in a withdrawal study design. Ninety percent (9/10) of tasimelteon-treated patients maintained entrainment, while only 20% (2/10) of placebo treated patients did so. In addition in the RESET study placebo randomized patients experienced significant deterioration in sleep and wake time measures by 74 minute (min) and 50 min respectively. In contrast, patients that continued on tasimelteon treatment experienced minimal changes in sleep and wake measures of 7 min and 9 min improvement respectively from baseline. The loss of entrainment and the loss of clinical improvements in placebo randomized patients were observed as early as the first month of the study.

In both the SET and RESET studies the effects on entrainment were seen both in the melatonin and cortisol rhythms, consistent with a tasimelteon effect at the SCN as a circadian regulator of the Master clock.

## Tasimelteon was shown to be safe and well tolerated in over 1300 patients, 111 treated for at least 6 months and 44 treated for over a year

More than 1300 individuals have been treated with at least one dose of tasimelteon, with doses up to 300 mg. The safety database includes 111 subjects treated for at least six months and 44 subjects treated for at least one year. At the time of the 120-day safety update for the NDA 139 patients have received 20 mg tasimelteon daily for at least 6 months, and 93 patients have received 20 mg tasimelteon daily for at least 1 year. A total of 429 unique patients were treated with daily doses of 20 mg tasimelteon in placebo-controlled studies. Common adverse events (≥2% in tasimelteon and greater than placebo) in placebo controlled studies (tasimelteon n=429, placebo n=203) included, (tasimelteon %, placebo %), Back pain (2.1%, 2.0%), Dreams (vivid or unusual), (2.6%, 0.5%), Diarrhea (2.3%, 1.0%), Dry Mouth (2.3%, 0.5%), Headache (9.6%, 7.4%), Nasopharyngitis (6.5%, 6.4%), Somnolence (3.0%, 1.5%), Upper Respiratory Tract Infection (2.6%, 1.5%). In placebo controlled studies (tasimelteon n=429, placebo n=203), all serious adverse events (SAEs) were deemed unrelated to study drug and the rates between tasimelteon and placebo treated patients were similar (1.6%, 1.5%). A similar tolerability profile was seen in the indicated population of totally blind patients with Non-24-Hour Disorder.

## Tasimelteon has a favorable benefit risk profile in the treatment of Non-24 as a Circadian Regulator, entraining the circadian clock and meaningfully improving clinical outcomes.

Tasimelteon's efficacy in the treatment of totally blind patients with Non-24 was demonstrated in two pivotal studies. Entrainment of the Master clock to a 24-hour rhythm was established with measures of both melatonin and cortisol rhythms. Tasimelteon was also shown to

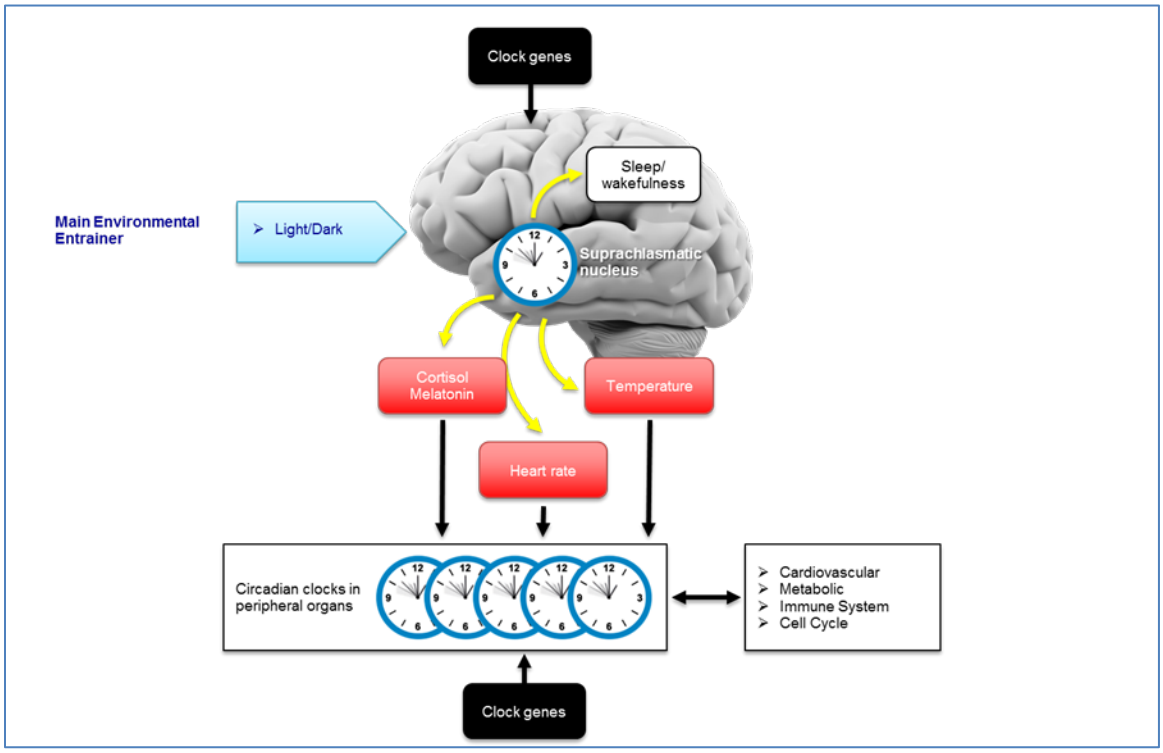
significantly and meaningfully improve sleep and wake measures and measures of global functioning. The side effect profile of tasimelteon was shown to be mild and coupled with a short half-life of about 1.5 hours, suggests that tasimelteon is well suited as a chronic treatment in this patient population. Overall tasimelteon presents a favorable benefit risk profile in the treatment of totally blind patients affected by Non-24, a serious and debilitating disorder.

# 2. NON-24-HOUR DISORDER OVERVIEW

## 2.1. The Circadian Timing System and the Suprachiasmatic Nucleus

Circadian rhythms are regulated by an internal timing system. This Circadian Timing System (CTS) is composed of the hypothalamic pacemaker the SCN, an array of SCN outputs, and a system of molecular clocks in peripheral tissues (1, 2). The SCN receives input from the retina, via a set of specialized intrinsically photosensitive Retinal Ganglion Cells (ipRGCs) through the retinohypothalamic tract (RHT) (3). Through this input the SCN is synchronized to a 24-hour light-dark cycle, and in turn through a system of endocrine, neuronal and physiological signals it entrains/synchronizes the peripheral clocks to a 24-hour rhythm. (Figure 1) The SCN controls key circadian rhythms of melatonin, cortisol and core body temperature. The SCN also controls the prototypical circadian rhythm of the rest-activity and sleep-wake cycle. Through the synchronization of peripheral clocks the SCN governs the optimal timing of key physiological processes including those of cardiovascular, metabolic and immune regulation (4-7).

**Figure 1: The Circadian Clock**



The core molecular components of the Circadian Timing System are beginning to be understood through numerous genetic and molecular studies conducted over the last twenty years. (8-11). This molecular machinery is well conserved across species and organized in a highly regulated hierarchical system of molecular feedbacks. The key molecules of the molecular clock fall in two classes, transcriptional activators and repressors. The transcriptional activators, BMAL1 and CLOCK, interact with each other forming complexes which in turn bind E-box cis elements in the promoter regions of target genes (12). The repressor molecules include the PERIOD (Per1, Per2, Per3) and CRYPTOCHROME (Cry1, Cry2) families of proteins. These molecules interact with the BMAL1:CLOCK complexes to block downstream transcription of target genes. These interactions set in motion a cyclical activation transcription process giving the oscillator its ability to keep time. Gene expression experiments have identified thousands of genes that are under circadian control comprising as much as 10% of the total genome.

The most powerful synchronizer (zeitgeber) of the Circadian Timing System is the light-dark cycle (2, 13). Light sensed by the retina rods and cones allows for the formation and perception of images. Light sensed by the ipRGCs provides information of the light-dark cycle to the SCN setting in motion a molecular system that synchronizes (entrains) the SCN to the 24-hour light-dark cycle (13).

## 2.2. Non-24-Hour Disorder in the Totally Blind

Totally blind people that cannot sense light due to either destruction of the ipRGCs or because of bilateral enucleation, are unable to entrain the Circadian Timing System at the SCN. As a result, the SCN continues to oscillate at its own endogenous rate which for most people is at a period longer than 24 hours. In totally blind people this period ($\tau$) is on average 24.5 hours, although there is considerable inter individual variability. This variable period length ($\tau$) results in corresponding varying lengths of circadian cycle lengths. Circadian cycle length is determined as 24 hours / ($\tau$ – 24) and refers to the number of days it takes for the internal timing to be synchronized with the external timing (Table 1). For example, for a person with an internal period of 24.0 the length of Circadian Period Length will be equal to 1 day. For a person with an internal period of 24.5, the Circadian Period Length will be equal to 48 days.

**Table 1: Circadian Period (τ) and the Corresponding Daily Phase Delay and Cycle Length**

| Circadian Period (τ) (hours) | Daily Phase Delay (mins) | Length of Circadian Cycle (days) |
|---|---|---|
| 24.1 | 6 | 240 |
| 24.2 | 12 | 120 |
| 24.3 | 18 | 80 |
| 24.4 | 24 | 60 |
| 24.5 | 30 | 48 |
| 24.6 | 36 | 40 |
| 24.7 | 42 | 34 |
| 24.8 | 48 | 30 |

Daily phase delay: [(τ -24.0 hours/1 day) *60 mins/hour]; Circadian cycle [24 hours ÷ (τ -24.0 hours)/ 1 day].

Non-24-Hour Disorder is a disorder of the Circadian Timing System which fails to entrain to the 24-hour light-dark cycle. Patients with Non-24 exhibit non-entrained rhythms of melatonin, cortisol, core body temperature and the rest-activity cycle. While it is expected that all peripheral clocks that control metabolic, cardiovascular, immune and other processes are also non-entrained, the clinical characterization of such a deregulation is not fully understood at this time. Patients present with a chronic sleep complaint that may include severely disrupted nighttime sleep and forced daytime sleep episodes which may occur with a cyclical pattern. As a result of this severe disruption of the sleep-wake timing, patients experience severe impairment in social and occupational functioning given the inability to schedule activities to a 24-hour day cycle (14).

Non-24-Hour Disorder should be suspected in any totally blind individual who presents with a chronic history of a severe sleep-wake disorder. More than half and as many as seventy percent of the totally blind patients are expected to have Non-24, making the disorder one of the most prevalent conditions among the totally blind with an estimated prevalence in the U.S. of approximately 80,000 individuals (15).

Non-24-Hour Disorder was first described by Remler in Germany in 1948 (16). Subsequent reports of the disorder established that both circadian rhythms of hormones and the rest-activity cycle were coincidently deregulated, pointing to a dysfunction of the Circadian System. The discovery of the ipRGCs in the retina established an anatomical basis for the disorder, explaining the high prevalence among the totally blind. Descriptions of the disruption of the sleep-wake cycle also shed light into the variable expression of the disorder, demonstrating that while some patients may have unscheduled sleep episodes that are delayed every day, most patients have a

scheduled albeit severely disrupted sleep episodes with compulsory daytime sleep episodes of variable length.

While more than 60 years have passed since the first description of the disorder, there is no treatment available and the disorder is under diagnosed and often misdiagnosed. Patients have been left either untreated or treated inappropriately. Sleep promoting agents are usually the first to be tried, as the disorder is misdiagnosed as a chronic insomnia. These sleep promoting agents are ineffective and they can result in additional disruption. The reason for this ineffectiveness is that sleep agents may temporarily address the homeostatic needs for sleep but not the circadian drive. The homeostatic drive refers to the drive for sleep which increases as the time from the last sleep episode increases. The circadian drive refers to the Circadian Timing System that controls the timing of the rest-activity cycle. Similarly, while many patients have used the dietary supplement melatonin they find this agent also inconsistent and generally ineffective. The reason for this is that the dietary supplement does not have the pharmacological properties to provide a consistent therapeutic effect needed for this chronic disorder.

Our extensive clinical program has demonstrated that tasimelteon possesses the necessary molecular, pharmacokinetic and pharmacodynamic properties to deliver a consistent and specific therapeutic effect for the treatment of Non-24 in the totally blind and therefore become the first treatment for the disorder in more than 60 years since the first description of Non-24 in 1948.

# 3. TASIMELTEON OVERVIEW

## 3.1. Chemical Structure (CS)

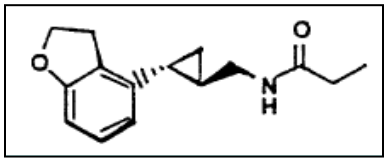
**Previous Product Names:** VEC-162 and BMS-214778

**Chemical Name:** (1R, 2R)-N-[2-(2,3-Dihydrobenzofuran-4-yl)cyclopropylmethyl]propanamide

**Molecular formula:** $C_{15}H_{19}NO_2$

**Molecular weight:** 245.32

**Figure 2: Chemical structure of tasimelteon**




## 3.2. Mechanism of Action (MoA)

### 3.2.1. Receptor Binding Affinity

Tasimelteon is a circadian regulator that resets the Master clock in the SCN of the hypothalamus by binding to both melatonin $MT_1$ and $MT_2$ receptors making it a **D**ual **M**elatonin **R**eceptor **A**gonist (DMRA). Tasimelteon's binding affinity for $MT_2$ is 2.1 to 4.4 times greater than to $MT_1$ (Table 2). Tasimelteon's main metabolites (i.e., M3, M9, M11, M12, M13, and M14) also bind to the melatonin receptors but with less affinity than the parent (Table 2). Tasimelteon and its main metabolites have no appreciable affinity for more than 160 other pharmacologically relevant receptors. This includes the GABA receptor complex, the binding site for sedative hypnotics, and receptors that bind neuropeptides, cytokines, serotonin, noradrenaline, acetylcholine, and opiates.

**Table 2: Comparative affinity of tasimelteon and its metabolites for the human melatonin $MT_1$ and $MT_2$ receptors**

| Compound | $MT_1$ | | $MT_2$ | | Ratio $K_i$ $MT_1$/ $K_i$ $MT_2$ |
|---|---|---|---|---|---|
| | $IC_{50}$ (nM) | $K_i$ (nM) | $IC_{50}$ (nM) | $K_i$ (nM) | |
| Tasimelteon | 0.586 | 0.304<br>0.350[a] | 0.133 | 0.0692<br>0.170[a] | 4.4<br>2.1 |
| M3 | 3,370 | 1,750 | 360 | 180 | 9.7 |
| M9 | 2,260 | 1,180 | 139 | 71.9 | 16.4 |
| M11 | 481 | 250 | 6.63 | 3.44 | 72.7 |
| M12 | 261 | 136 | 20.8 | 10.8 | 12.6 |
| M13 | 7.69 | 4 | 1.78 | 0.922 | 4.3 |
| M14 | 198 | 103 | 8.42 | 4.37 | 23.6 |

$IC_{50}$ = Concentration producing 50% inhibition; Ki= dissociation constant for the inhibitor.

## 3.3. Physiologic Effects (PE)

Tasimelteon has demonstrated full physiologic effects of a circadian regulator in non-clinical and clinical studies of circadian challenge.

### 3.3.1. Non-clinical studies demonstrating that tasimelteon shifts and entrains circadian rhythms

A non-clinical *ex vivo* study (Study 52254) demonstrated that administration of 5 mg/kg tasimelteon causes a significant shift (1.4 hours) of the SCN electrical activity rhythm.

An acute *in vivo* administration study (Study 52274) demonstrated that administration of a single dose of 1.0 or 5.0 mg/kg of tasimelteon shift activity rhythms of “free- running” rats. Lower doses of tasimelteon (0.01 and 0.1 mg/kg) had no effect on the phase of the circadian rhythm.

A chronic *in vivo* study (Study 52273) demonstrated that 1 and 5 mg/kg doses of tasimelteon entrained the circadian activity rhythms of 91% and 100% of “free-running” rats, respectively. The lower tasimelteon doses, 0.01 and 0.1 mg/kg, entrained 11% and 25% of the rats, respectively. These results indicate that tasimelteon produces a dose-dependent entrainment of “free-running” circadian rhythms.

The estimated pharmacological effective dose in man based on these 3 animal studies is 0.14 to 0.71 mg/kg, or about 10 mg to 50 mg in a 70 kg patient on the basis of surface area.

### 3.3.2. Clinical Evidence of dose/exposure effectiveness in shifting circadian rhythms

Study 2101 was a randomized, double-blind, parallel, placebo-controlled, in-patient study in a light controlled time isolation sleep facility that assessed the safety and efficacy of four oral doses of tasimelteon (10-, 20-, 50-, and 100 mg) compared to placebo. Subject's sleep schedule was abruptly advance by 5 hours, a protocol which severely disrupts circadian rhythms including those of melatonin and the sleep-wake cycle. Circadian rhythms, sleep parameters, and subject alertness were assessed during an 8-day inpatient stay. Tasimelteon was shown to phase advance circadian rhythms on the first night of treatment in a dose dependent manner as measured by a shift in Dim Light Melatonin Onset (17).

The results of this study provided evidence that tasimelteon has the ability to phase advance the circadian rhythm of melatonin secretion in a dose-dependent manner with the 20 mg being the minimum dose at which circadian phase shifting was observed.

### 3.3.3. Clinical Evidence of dose/exposure effectiveness in sleep measures

Study 2101 showed that tasimelteon minimized the disruption in sleep efficiency caused by the 5 hour phase advance protocol in a dose-related manner. At the time of maximum sleep disruption in the middle third of the night, tasimelteon significantly minimized the sleep disruption as compared to placebo. The mean change from baseline in the 2$^{nd}$ third of the night sleep efficiency by dose is listed in Table 3. The p-value (in parentheses) compares that dose group to placebo using ANOVA with contrasts.

**Table 3: Change in sleep efficiency between Night 4 and Night 2 by dose (Study 2101)**

| Dose | Mean Change % ± SD in Sleep Efficiency |
|---|---|
| | 2nd Third of the Night (p-value) |
| Placebo (N=7) | -34.92 ± 38.23 |
| 10 mg tasimelteon (N=8) | -12.64 ± 13.83 (0.0303) |
| 20 mg tasimelteon (N=8) | -5.11 ± 12.78 (0.0048) |
| 50 mg tasimelteon (N=7) | -2.10 ± 4.14 (0.0028) |
| 100 mg tasimelteon (N=7) | -2.30 ± 5.72 (0.0030) |

Values for change in sleep efficiency (mean ± SD) are displayed for each dose group. The p-value (in parentheses) compares that dose group to placebo using ANOVA with contrasts.

Study 3101 a transient insomnia study in 412 healthy subjects with a 5-hour sleep timing advance showed significant improvement in both objective latency to persistent sleep (LPS) and wake after sleep onset (WASO) at 20 mg and 50 mg of tasimelteon [LPS=21.5 ($p<0.001$) and 26.3 min ($p<0.001$), for 20 and 50 mg respectively; WASO= 24.2 min ($p=0.017$) and 33.7 min ($p=0.001$), for 20, and 50 mg respectively].

### 3.3.4. Dose Selection

The results of Study 2101 and Study 3101, taken together demonstrate that 20 mg is the minimum effective dose regulating circadian rhythms and improving sleep parameters when there is circadian misalignment between the endogenous rhythm and the desired sleep timing. Due to the rarity of the Non-24 condition and the challenges enrolling patients into pivotal clinical trials, testing more than one dose level was not feasible.

## 3.4. Non-clinical Development Program

Tasimelteon has been developed as a circadian regulator for the treatment of Non-24 in the totally blind.

The non-clinical Pharmacology and Pharmacokinetics have been characterized and indicate that tasimelteon is a selective and potent dual melatonin receptor agonist (DMRA), capable of shifting and entraining circadian activities, and is rapidly absorbed and extensively metabolized in animals.

Toxicological effects were limited and seen primarily at excessive exposures or concentration levels that would not be relevant at the expected therapeutic dose. Tasimelteon showed no significant reproductive toxicity and did not cause malformations or selective embryo toxicity. Tasimelteon showed no significant genotoxic effects and no carcinogenic findings at clinically relevant exposures. Furthermore, tasimelteon did not show potential for abuse liability.

The non-clinical program supports the clinical use of tasimelteon at the anticipated therapeutic dose for the treatment of Non-24 in the totally blind.

### 3.4.1. Non-Clinical Pharmacology

The results of the pharmacological studies indicated that tasimelteon is a circadian regulator with specific agonist activity at both melatonin receptors, capable of shifting and entraining circadian activity.

Tasimelteon showed a full agonist activity at both $MT_1$ and $MT_2$ receptors but no significant interaction with other commonly screened receptor or enzyme binding sites, including receptors of neurotransmitter systems associated with abuse potential such as dopamine, norepinephrine, serotonin, gamma-aminobutyric acid (GABA), acetylcholine, opioid, N-methyl-D-aspartate (NMDA), and cannabinoid. Tasimelteon exhibited a greater affinity for the $MT_2$ as compared to the $MT_1$ receptor. The affinity of the main tasimelteon metabolites for the $MT_1$ and $MT_2$ receptors is at least 10 fold lower than the affinity of the parent compound for these receptors. As with tasimelteon, binding of the metabolites to the $MT_1$ and $MT_2$ receptors was shown to be very selective as there was no other significant affinity with more than 160 other pharmacologically relevant receptors.

The circadian regulatory potential of tasimelteon was further demonstrated in three studies, where tasimelteon was able to shift the peak of the SCN electrical activity rhythm of rats, and was shown to shift and to entrain the onset of the running-wheel activity of rats with "free running" circadian rhythms.

### 3.4.2. Non-Clinical Pharmacokinetics

Absorption, distribution, metabolism, and excretion (ADME) studies were conducted *in vitro* and *in vivo* with mice, rats, rabbits, and monkeys, and evaluated oral or i.v. administration of tasimelteon following single and multiple doses for up to 29 days. Doses of tasimelteon administered to the animal species ranged from 0.25 mg/kg to 600 mg/kg in these studies.

ADME profiles of tasimelteon were variable among the species. Oral bioavailability was approximately 58 % in rats and 11.7% in monkeys. Evaluation of mean brain/plasma concentration ratio in rats suggests that tasimelteon may pass through the blood brain barrier rapidly. Tasimelteon was rapidly distributed to most rat tissues within 1 hour after a single oral dose and eliminated mainly through the urinary route; the highest drug concentrations were observed in the plasma, liver, kidneys, and gastrointestinal system. Tasimelteon was shown to be moderately bound to proteins in human and animal serum.

In human, CYP1A2 and CYP3A4 are the major isozymes involved in the metabolism of tasimelteon; CYP1A1, CYP2C9/C19, and CYP2D6 also minimally contribute to the metabolism of tasimelteon. *In vivo* metabolic pathways in mice, rats, and monkeys revealed that tasimelteon was extensively metabolized in all species tested. The main human tasimelteon metabolites were shown to be present in non-clinical species.

### 3.4.3. Non-Clinical Toxicology

The toxicological profile of tasimelteon has been evaluated in 35 studies. These include 4 single oral dose studies in mice (100 to 1,750 mg/kg), rats (50 to 400 mg/kg, and 100 to 1,750 mg/kg), and monkeys (10 to 200 mg/kg) and 8 repeated oral dose studies including a three-month oral range-finding study in mice (25 to 800 mg/kg), a two-week oral exploratory study in rats (50 to 400 mg/kg), a one-month oral toxicity study in rats (25 to 400 mg/kg), a 4-week toxicokinetics study in rats (25 to 500 mg/kg), a six-month oral toxicity study in rats (5 to 500 mg/kg), a one-week oral range-finding study in monkeys (25 to 175 mg/kg), a one-month oral toxicity study in monkeys (15 to 125 mg/kg), and a one-year oral toxicity study in monkeys (3 to 150 mg/kg). The toxicokinetics of the main human metabolites after the oral administration of tasimelteon to rats, mice, and rabbits was also determined in several independent multiple dose studies to support the non-clinical data.

There were 3 *in vitro* studies (Ames Reverse-mutation studies in *Salmonella typhimurium* and *Escherichia coli*, and a cytogenetics study in Primary Human Lymphocytes) and 1 *in vivo* genotoxicity study (micronucleus evaluation from a one-month oral toxicity study in rats at 25, 100, or 400 mg/kg) performed with tasimelteon, and 2 *in vitro* genotoxicity assays conducted with the human metabolite M11. Two long term carcinogenicity studies were conducted in mice (104 weeks at 30, 100, and 300 mg/kg) and rats (104 weeks at 20, 100, and 250 mg/kg), with one additional supportive toxicokinetics study.

Eight studies were conducted to evaluate the reproductive and developmental toxicity of tasimelteon in rats and rabbits, including a study of fertility and early embryonic development in rats (5, 50 and 500 mg/kg), two embryo-fetal development study in rats (5, 50 and 500 mg/kg), and rabbits (5, 30, and 200 mg/kg), a study of prenatal and postnatal development in the rat (50, 150 and 450 mg/kg), and 4 dose range finding or supportive toxicokinetics studies.

Two local tolerance studies evaluated skin toxicity in guinea pigs and ophthalmic irritation using an *in vitro* bovine corneal assay.

Two studies evaluated the abuse potential of tasimelteon with oral and intravenous (i.v.) administration using rats, with an additional supportive study to determine systemic concentrations of tasimelteon after i.v. administration.

Another study determined the molar extinction coefficient for tasimelteon and its metabolites for the consideration of photosafety.

Acute and repeated-dose toxicity studies in non-clinical species indicate that, at clinically relevant exposures, the general organ toxicity of tasimelteon was overall limited. Findings were fully or partially recovered after a non-dosing period.

Tasimelteon was not mutagenic or clastogenic *in vitro* and not genotoxic *in vivo*. Two-year carcinogenicity studies conducted in rats and in mice did not reveal any carcinogenic findings at clinically relevant exposures for humans.

In reproductive and developmental toxicity studies tasimelteon showed no significant reproductive toxicity and did not cause malformations or selective embryo toxicity.

Tasimelteon was classified as a mild irritant in a bovine corneal opacity and permeability assay, and showed no evidence of inducing skin sensitivity in guinea pigs.

A drug-discrimination study and a self-administration study were conducted in rats using as comparator the benzodiazepine midazolam, a compound with known abuse liability. These studies showed that animals did not recognize the stimulus effects of orally administered tasimelteon as similar to the midazolam training cue, and that i.v. self-administration did not function as a reinforcer similar to midazolam. These results indicate a lack of potential for abuse liability, consistent with the selective receptor binding profile of tasimelteon.

### 3.4.4. Non-Clinical Conclusions

The results of the non-clinical studies support the following conclusions:

- tasimelteon has circadian regulator activity,
- oral tasimelteon is rapidly absorbed and extensively metabolized in animals, with ADME profiles differing between species,

- oral tasimelteon exposure was associated with limited target organ toxicity at relevant exposures, and findings were fully or partially recovered after a non-dosing period,
- tasimelteon showed no significant genotoxic effects, with carcinogenic findings at exposures which were not clinically relevant and therefore of unknown human relevance,
- tasimelteon showed no significant reproductive toxicity and did not cause malformations or selective embryo toxicity,
- tasimelteon was a mild ocular irritant but showed no evidence of inducing skin sensitivity,
- tasimelteon did not show potential for abuse liability, and
- the main human tasimelteon metabolites were shown to be present in non-clinical species.

In summary, the non-clinical program supports the clinical use of tasimelteon at the anticipated therapeutic dose for the treatment of Non-24 in the totally blind. The toxicological effects were seen primarily at excessive exposures or concentration levels that would not be relevant at the expected clinical dose.

## 3.5. Clinical Pharmacology

The tasimelteon clinical pharmacology program comprised of fourteen (14) phase I clinical pharmacology studies including single and multiple ascending dosing studies, renal and hepatic dysfunction studies, food effect study, ethanol effect study, an ADME study, a thorough QT study, and four drug-drug interaction (DDI) studies. Further, a modeling population PK analysis (using data from four clinical pharmacology studies -Study 1105, Study 1106, Study 1107, and Study 1110) was conducted to examine the effects of intrinsic and extrinsic factors on the PK of tasimelteon.

A complete list of the studies conducted for the development of tasimelteon including the Clinical Pharmacology studies can be found in Appendix A – Listing of Tasimelteon Clinical Studies.

### 3.5.1. Pharmacokinetics of Tasimelteon

The observed mean elimination half-life for tasimelteon is 1.32 ± 0.43 hours. The mean terminal elimination half-life ± standard deviation of the main metabolites ranges from 1.26 ± 0.48 to 3.67 ± 2.22 hours. The pharmacokinetics of tasimelteon and its metabolites did not change with repeated daily dosing. The pharmacokinetics of tasimelteon is linear over doses ranging from 1 to 300 mg.

#### 3.5.1.1. Absorption

Tasimelteon is absorbed rapidly, with median peak concentration ($T_{max}$) occurring at approximately 0.5 hours after fasted oral administration. Total oral absorption of tasimelteon is at least 80.4%. The absolute bioavailability of tasimelteon in humans has not been determined but oral bioavailability was estimated to be 58% in rats and 11.7% in monkeys (Section 3.4.2).

Administration of tasimelteon with a high fat/high calorie meal resulted in a reduction of $C_{max}$ by 44%. The median $T_{max}$ increased from 0.75 hours under fasted conditions to 2.5 hours under fed conditions. $AUC_{(0\text{-}t)}$ and $AUC_{(inf)}$ were comparable under fed and fasted conditions, 108.57% and 106.54%, respectively, and 90% confidence intervals contained within the 80% to 125% equivalence window. In phase III efficacy studies (SET and RESET), tasimelteon was administered without regard to the timing of meals. In conclusion, tasimelteon can be administered without regard to meals.

#### 3.5.1.2. Distribution

The apparent oral volume of distribution at steady state of tasimelteon in young healthy subjects is approximately 59 - 126 L. At therapeutic concentrations, tasimelteon is 89% – 90% bound to proteins.

#### 3.5.1.3. Metabolism

When administered orally, tasimelteon undergoes a rapid metabolism through the CYP450 system at the gastrointestinal level and in the liver. The metabolic pathway is displayed in Figure 3.

Metabolism of tasimelteon consists primarily of oxidation at multiple sites and oxidative dealkylation resulting in opening of the dihydrofuran ring followed by further oxidation to give a carboxylic acid. CYP1A2 and CYP3A4 are the major isozymes involved in the metabolism of tasimelteon. CYP1A1, CYP2D6, CYP2C19, and CYP2C9 also minimally metabolize tasimelteon. Phenolic glucuronidation is the major phase II metabolic route.

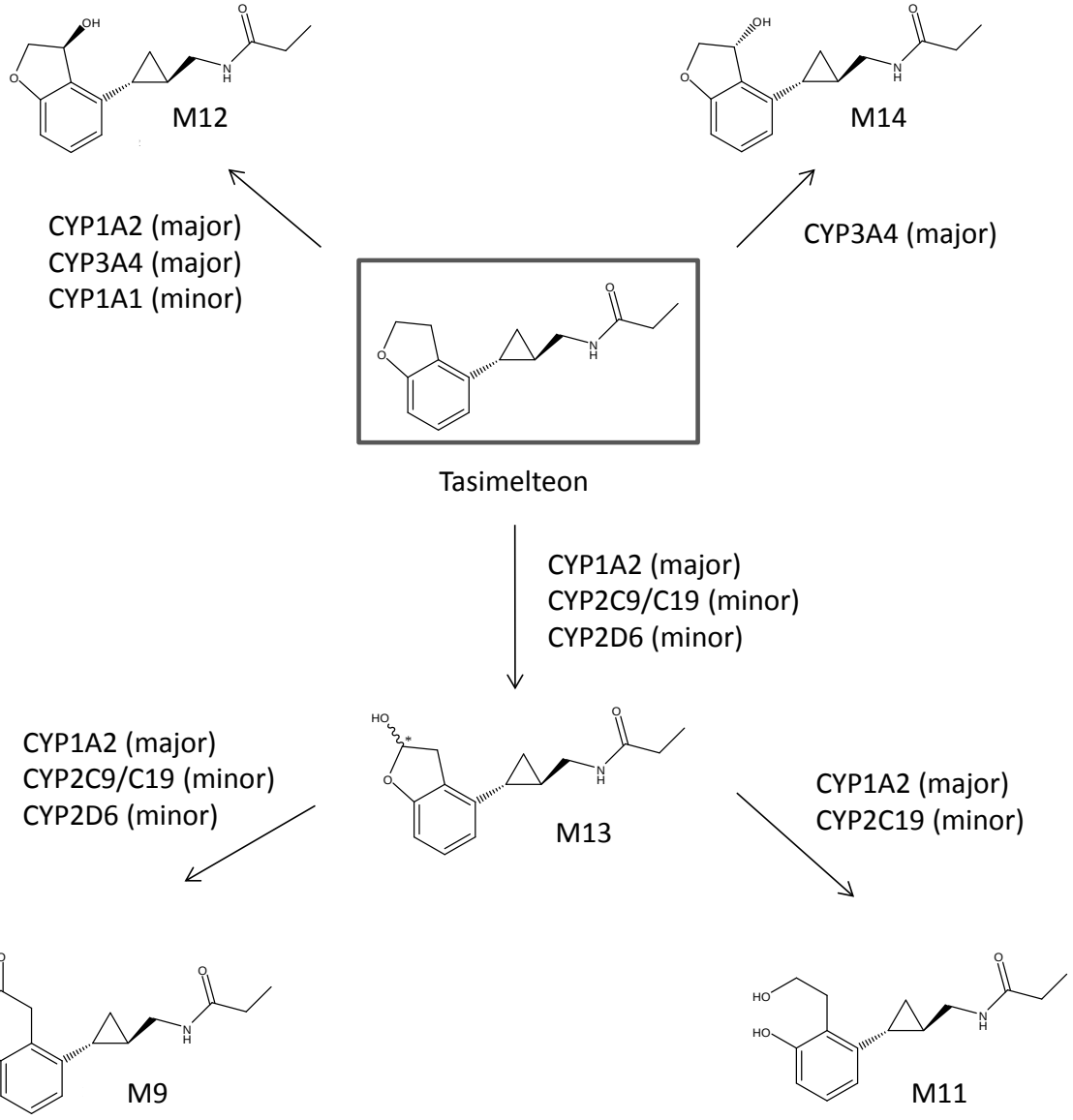
A global assessment of tasimelteon pharmacokinetics was done by analyzing 115 subjects in 5 studies (Study 1105, Study 1106, Study 1107, Study 1110, and Study 1112) and is summarized in Table 4. Tasimelteon's main metabolites and their ratios of AUCs over the parent in human plasma are M12, 1.6; M13, 0.96; M9, 0.92; M11, 0.38 and M14, 0.05 (Table 4). These metabolites are formed and eliminated rapidly.

**Table 4: Global Descriptive Statistics for PK Parameters of Tasimelteon and Metabolites**

| | **Tasimelteon** | **M3**[a] | **M9** | **M11** | **M12** | **M13** | **M14** |
|---|---|---|---|---|---|---|---|
| $C_{max}$ (ng/mL) | 234.9 ± 127.7 | 133.2 ± 52.7 | 238.7 ± 96.7 | 49.5 ± 16.3 | 96.5 ± 28.4 | 288.8 ± 93.9 | 6.4 ± 3.3 |
| $T_{max}$ (h) | 0.500 | 0.500 | 0.750 | 1.000 | 1.000 | 0.500 | 0.750 |
| AUC (h×ng/ml) | 411.4 ± 327.8 | 220.4 ± 62.3 | 379.4 ± 105.8 | 155.8 ± 64.0 | 655.2 ± 349.7 | 393.7 ± 138.7 | 22.0 ± 20.1 |
| T½ (h) | 1.32 ± 0.4 | 3.67 ± 2.2 | 1.41 ± 0.4 | 2.02 ± 0.6 | 3.33 ± 1.3 | 1.26 ± 0.5 | 2.0 ± 1.0 |

[a] Assayed in 3 studies: Study 1106, 1107, and 1111.
Arithmetic mean ± standard deviation is reported for all criteria except $T_{max}$ for which the median is reported.

**Figure 3: Metabolic pathway for tasimelteon as determined in human liver microsomes**




### 3.5.1.4. Excretion

Following oral administration of radiolabeled tasimelteon, 80.4% of total radioactivity was excreted in urine and approximately 3.72% in feces, resulting in a mean recovery of 84.1%. Less than 1% of the dose was excreted in urine as the parent compound.

Repeated once daily dosing with tasimelteon does not result in PK parameter changes or significant accumulation owing to the short half-life of tasimelteon.

### 3.5.2. Intrinsic or Extrinsic Factors

#### 3.5.2.1. Intrinsic Factors

Exposure to tasimelteon was increased approximately 2-fold in subjects with hepatic impairment after a single 20 mg/day dose. Based on the observed inter-subject variability in the PK parameter of tasimelteon, this result is not clinically relevant and dose adjustment is not necessary in patients with mild or moderate hepatic impairment. Tasimelteon has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

Consistent with the lack of renal excretion as a pathway of elimination for tasimelteon, there was no apparent relationship between tasimelteon CL/F and renal function as measured by either creatinine clearance (CLcr) or estimated glomerular filtration rate (eGFR). Based on these results, a dose reduction is not deemed necessary.

No dose adjustment is necessary based on age, gender, or body mass index (BMI) as multivariate and population PK analysis showed that the contribution of these factors to tasimelteon overall variability, if present, is small and not clinically relevant.

Clinical study 1103, a thorough QT study, was a four-period, randomized, double-blind, multiple-dose, crossover study. Forty healthy men and women were treated in a random order with 20 mg tasimelteon, 300 mg tasimelteon, placebo, and 400 mg Moxifloxacin (unblinded positive control). Results of this cardiac safety study demonstrate that tasimelteon has no potential to affect cardiac repolarization.

#### 3.5.2.2. Extrinsic Factors

##### 3.5.2.2.1. Potential Effects of Other Drugs on Tasimelteon

**Fluvoxamine (strong CYP1A2 inhibitor):** When fluvoxamine 50 mg/day was administered for 6 days prior to single-dose co-administration of 5.667 mg tasimelteon and 50 mg fluvoxamine, the $AUC_{0\text{-}inf}$ for tasimelteon increased approximately 7-fold, and the $C_{max}$ increased approximately 2-fold, compared to tasimelteon administered alone. Tasimelteon should be administered with caution in combination with fluvoxamine or other strong CYP1A2 inhibitors.

**Ketoconazole (strong CYP3A4 inhibitor):** When a single 20 mg dose of tasimelteon was administered on the fifth day of ketoconazole 400 mg per day administration, tasimelteon's exposure increased by approximately 54%, compared to administration of tasimelteon alone. No dose adjustment is recommended as the clinical significance of this change is unclear.

**Smoking (moderate CYP1A2 inducer):** When 20 mg tasimelteon was administered to twenty-four subjects who smoke at least 10 cigarettes per day, tasimelteon exposure decreased by approximately 40% as compared to the exposure in subjects who did not smoke. A dose adjustment may be considered.

**Rifampin (strong CYP3A4 and moderate CYP2C19 inducer):** When a single tasimelteon 20 mg dose was administered after 11 days of rifampin 600 mg administration, tasimelteon mean exposure was reduced by approximately 89%. Efficacy may be reduced when tasimelteon is used in combination with strong CYP3A4 inducers such as rifampin. A dose adjustment may be considered.

**Other inhibitors/inducers:** Co-administration of tasimelteon with CYP inducers or inhibitors of CYP1A1, CYP2C9/2C19, and CYP2D6 is not expected to alter plasma concentrations of tasimelteon. Based on in vitro studies, these CYP isoforms have minimal contribution to the metabolism of tasimelteon.

#### 3.5.2.2.2. Potential Effects of Tasimelteon on Other Drugs

**Midazolam (CYP3A4 substrate):** Administration of tasimelteon 20 mg QD for 14 days did not produce any clinically significant changes in the $T_{max}$, $C_{max}$, or AUC of midazolam or 1-OH midazolam after oral administration of 10 mg. This indicates that there is no induction of CYP3A4 by tasimelteon at this dose.

**Rosiglitazone (CYP2C8 substrate):** Administration of tasimelteon 20 mg QD for 16 days did not produce any clinically significant changes in the $T_{max}$, $C_{max}$, or AUC of rosiglitazone after oral administration of 4 mg. This indicates that there is no induction of CYP2C8 by tasimelteon at this dose.

**Other CYPs**: Neither tasimelteon nor its most abundant metabolites appear to induce CYP2B6 *in vitro*, except at high concentrations well above the average human maximum plasma concentrations at the 20 mg therapeutic dose.

#### 3.5.2.2.3. Tasimelteon and ethanol interaction

In an alcohol interaction study, tasimelteon had no additive effect on psychomotor performance or memory task. In healthy volunteers ethanol was co-administered with 20 mg of tasimelteon. Most of the impairments on pharmacodynamics measures were related to ethanol and not to the addition of tasimelteon.

# 4. CLINICAL DEVELOPMENT PROGRAM

Tasimelteon's efficacy and safety for the treatment of Non-24 in the totally blind is based on a complete clinical development program consisting of 22 clinical studies. Two pivotal efficacy studies SET and RESET were conducted to study tasimelteon in the treatment of totally blind patients with Non-24-Hour Disorder. An overview of the clinical studies can be found in Appendix A – Listing of Tasimelteon Clinical Studies.

Over 1600 patients and healthy volunteers (306:placebo, 1346:tasimelteon) have been studied. The tasimelteon clinical development program includes the largest comprehensive cohort of Non-24 patients in the world with over 180 patients treated with tasimelteon.

## 4.1. Study 2101 – Circadian Phase Shifting Proof of Mechanism

Study 2101, was a proof-of-concept circadian phase shifting study in healthy volunteers that demonstrated tasimelteon's ability to phase shift circadian rhythms, Section 3.3. This study provided evidence of proof of mechanism of tasimelteon as a circadian regulator. Specifically Study 2101 demonstrated that:

- Tasimelteon phase advanced circadian rhythms as measured by plasma melatonin on the first night of treatment;
- Tasimelteon minimized disruption in sleep efficiency, wake after sleep onset (WASO) and sleep latency.

## 4.2. Phase III Clinical Program in totally blind patients with Non-24-Hour Disorder

Tasimelteon's efficacy and safety profile in Non-24 patients is based on data from two controlled clinical trials and two open label safety studies. Two earlier Phase III trials in healthy volunteers and patients with primary insomnia further support the safety and efficacy of tasimelteon.

The efficacy of tasimelteon in treating Non-24-Hour Disorder in the totally blind is demonstrated by the following phase III studies:

- Study VP-VEC-162-3201 (**S**afety and **E**fficacy of **T**asimelteon: SET) a randomized, placebo-controlled, parallel study of the safety and efficacy of tasimelteon in totally blind individuals with Non-24-Hour (Section 6.1).
- Study VP-VEC-162-3203 (**R**andomized withdrawal study of the **E**fficacy and **S**afety of **T**asimelteon: RESET) a randomized, placebo-controlled withdrawal study in Non-24 patients that had responded to tasimelteon treatment (Section 6.2).

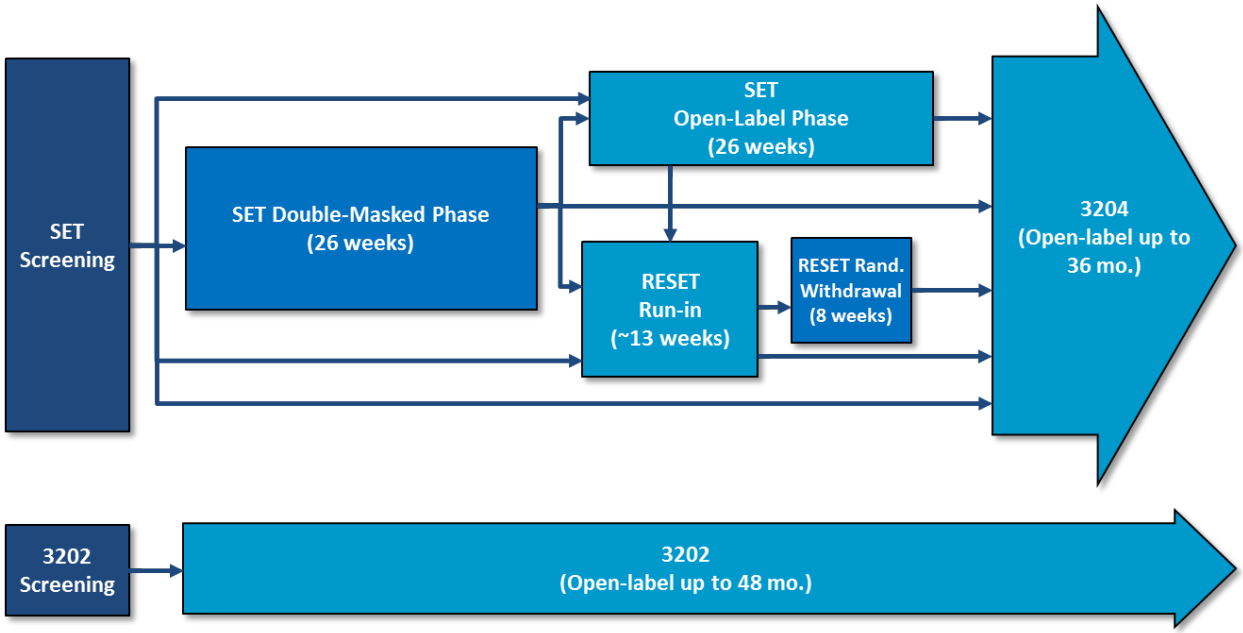
Given the challenges in recruiting patients for this rare orphan disorder and with approval by the Division of Neurological Products, patients that enrolled in the SET study were given the option of continuing participation in the RESET study. A flow diagram of patient trial participation is provided in Figure 4.

This unique program design allows for both the evaluation of efficacy through two independent clinical studies as well as the collection of information on the effects of initiating or discontinuing tasimelteon on individual patients over periods of time that exceeded 400 days for some patients.

The two open-label safety studies with tasimelteon are currently ongoing: Study VP-VEC-162-3202 in France and Study VP-VEC-162-3204 in the United States and Germany. Interim database locks from both of these studies were conducted and safety data through November 30, 2012 was included in the integrated safety database. A 120-day safety update with a cut-off date of July 10, 2013 from the ongoing studies indicated that there were no new findings that affect the conclusions of the integrated summary of safety described in Section 7.

Based on the safety database and clinical studies which met the prospectively claimed primary efficacy endpoints, Vanda believes that there is sufficient clinical evidence to demonstrate the safety and efficacy of tasimelteon.

**Figure 4: Tasimelteon Clinical Study Program in Patients with Non-24**



### 4.2.1. Pediatric Assessment

While pediatric assessments of the safety or efficacy of tasimelteon have not been conducted for this orphan disorder, Vanda plans to evaluate the feasibility of conducting a pediatric program in children and adolescents with Non-24.

# 5. CLINICAL TRIAL ENDPOINTS

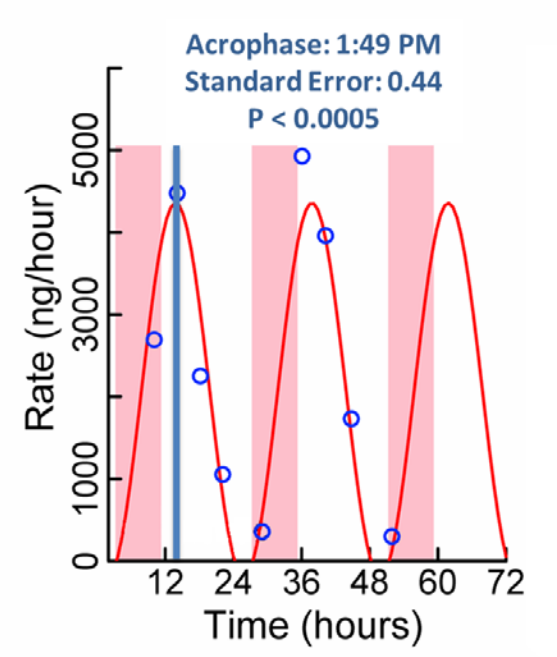
The Non-24-Hour clinical development program consists of two main types of endpoints, measures of entrainment and measures consisting of clinician-reported and patient-reported clinical responses. The endpoint of entrainment demonstrates efficacy in resetting the Master clock to 24 hours. The primary measure of clinical response is a composite endpoint referred to as the Non-24-Hour Clinical Response Scale (N24CRS) which measures improvements in sleep-wake endpoints and overall functioning.

## 5.1. Entrainment

Entrainment is a measure of synchronization of the Master clock to the 24-hour day. Entrainment can be measured by 2 distinct circadian rhythms: melatonin, (including its primary metabolite, 6-sulfatoxy-melatonin or aMT6s), and cortisol. These are established objective measures based on recognized analytes assessed in the urine with aMT6s being the gold standard in the field (18, 19).

Patients in the Non-24 studies collected urine voids over 48 hours in 4 hour intervals (8 hours overnight) and the aMT6s analyte concentration, volume and timing were recorded. The method used to determine the speed of an individual's endogenous Master clock, or $\tau$ (tau), is well established (13, 20-22). The Non-24 clinical development program has implemented this accepted method. A cosinor curve was fit to the data from each 48 hour period to determine the acrophase, or peak timing of analyte secretion. The goodness of fit was also calculated as a p-value and reported. An example showing both the raw data and the cosinor fit is shown in Figure 5.

**Figure 5: Acrophase Calculation**




This process is repeated weekly during the assessment period. In healthy individuals the acrophase time is constant and is in sync with the 24-hour day with melatonin peaking at night. In people suffering from Non-24, acrophase times, and the underlying melatonin and cortisol rhythms, move over time. The daily acrophase delay is based on the patient's τ.

**Table 5: Data from a Non-24 Patient Illustrate the Daily Delay in Acrophase Time**

| Week | Acrophase (Time) | SE (Hours) | p-value |
|---|---|---|---|
| 1 | 1:49 PM | 0.44 | <0.0005 |
| 2 | 5:23 PM | 0.43 | <0.0005 |
| 3 | 9:34 PM | 0.27 | <0.0005 |
| 4 | 3:01 AM | 0.57 | 0.001 |

SE = Standard Error

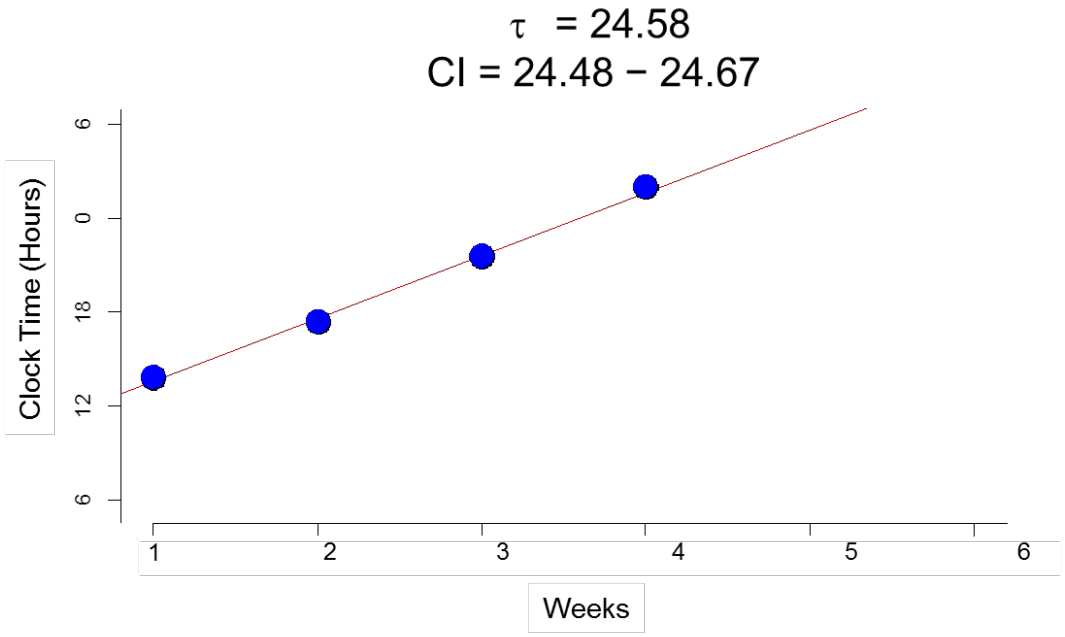
Table 5 shows data from a Non-24 patient who collected four 48 hour urine collections, each a week apart. For each of these collections, the acrophase was estimated and a p-value and standard error were estimated indicating the goodness of fit of the cosinor curve.

The Non-24 patient illustrated in Table 5 has acrophase times that move from 1:49 PM to 3:01 AM over the course of the four week assessment. To calculate τ, a linear regression across the weekly measures of acrophase is performed. The slope characterizes an individual's τ

represented by 24 + the slope. Entrained individuals maintain a constant daily acrophase, therefore the value of their slope would be zero translating to a τ = 24.0 hours.

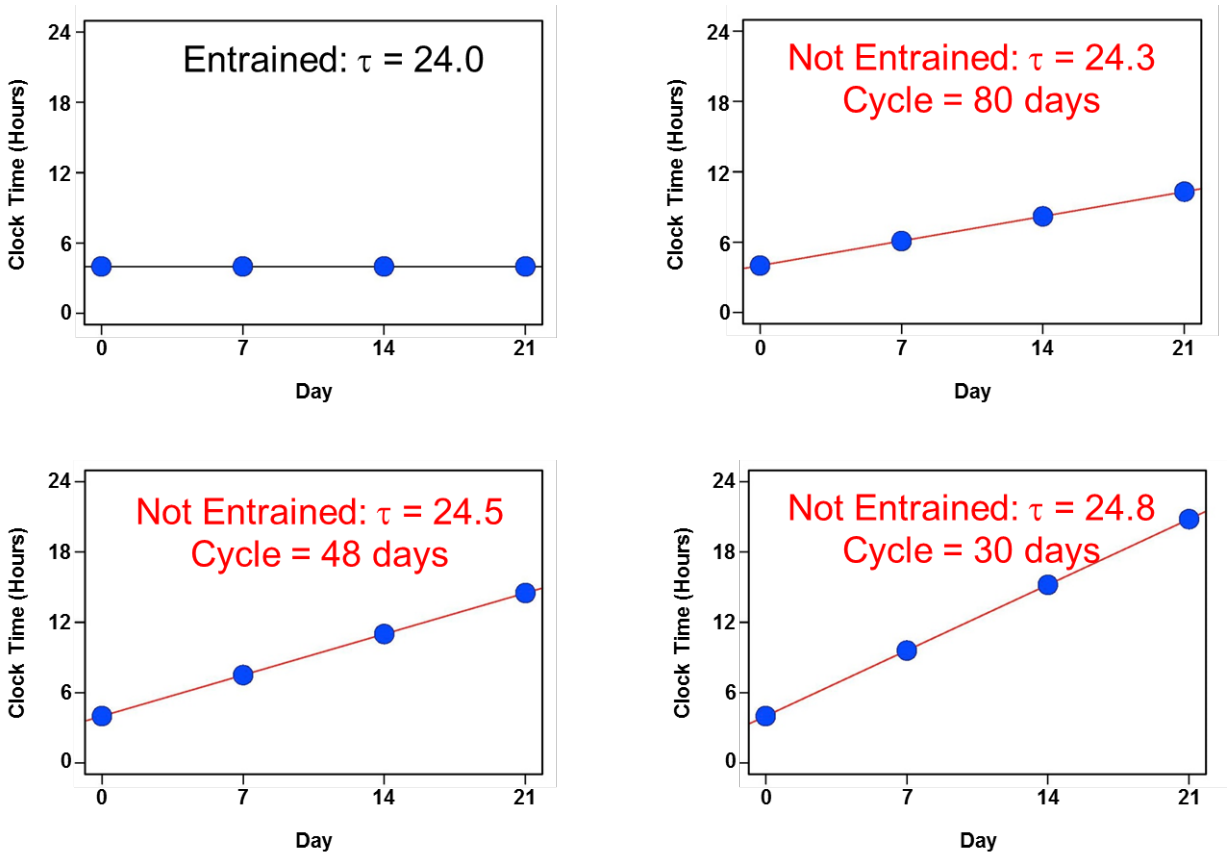
The linear regression for the patient's data in Table 5 is graphed in Figure 6 . The weekly acrophase values delayed over time, generating a slope greater than zero, reflecting the fact that this patient is not entrained. This Non-24 patient had a τ value of 24.58 hours (95% Confidence Interval (CI) 24.48 to 24.67), about 35 minutes longer than a 24-hour day. Since this endogenous rhythm delays 35 minutes every day, it takes 42 days to cycle back to their starting point. Therefore, this patient's circadian cycle is 42 days.

**Figure 6: Calculation of τ: Linear Regression Over Acrophase Points**



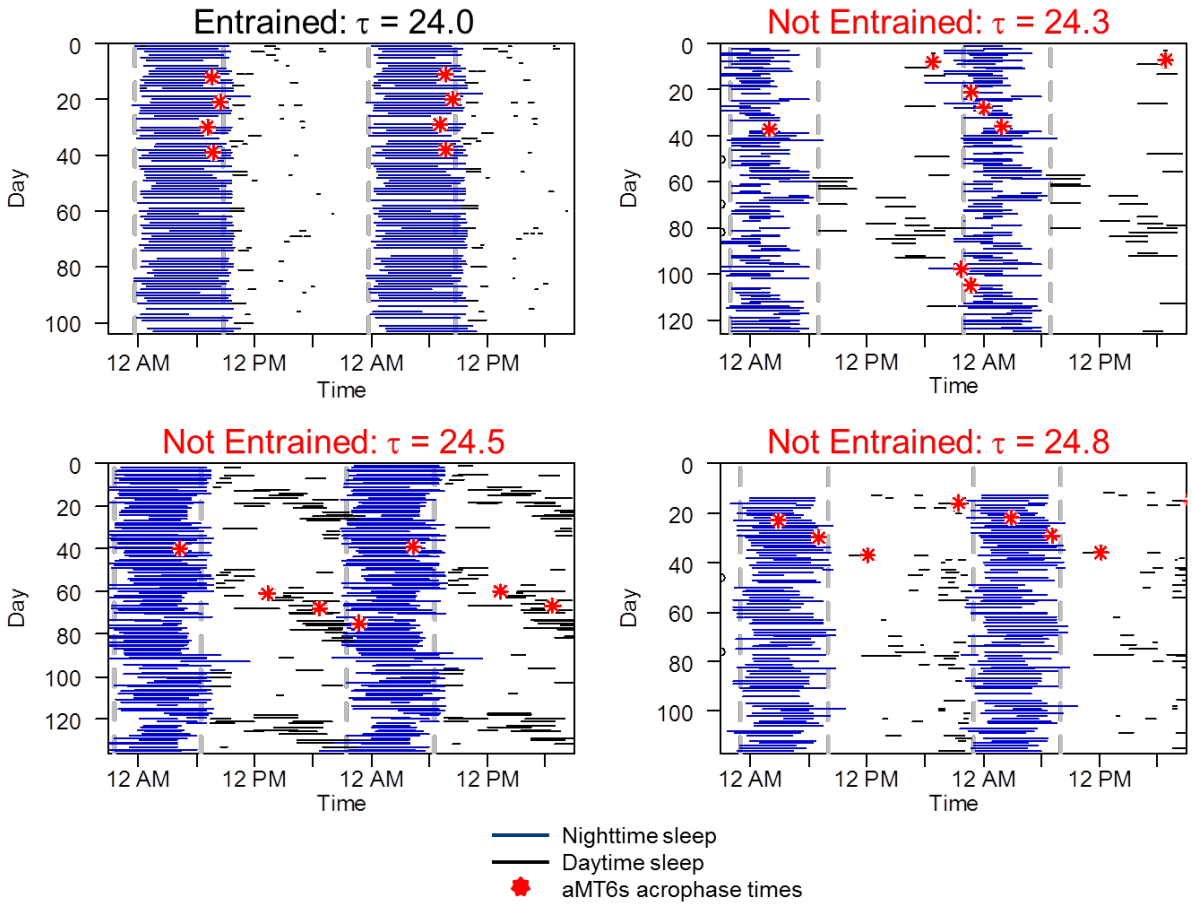

The points in the linear regression are weighted by the confidence of the estimate by taking the inverse of the squared standard error. The 95% confidence interval is listed as the CI in the figure. This provides an understanding of whether an individual is clearly different from entrained, i.e., their 95% CI does not include 24.0. Different people have different endogenous τ's and therefore different circadian cycles as shown in Figure 7.

**Figure 7: Composite of Four Different τ Values**




The upper left panel of Figure 7 shows an entrained individual (τ = 24.0). This reflects a healthy individual without Non-24 and is also the goal of effective treatment for this disorder. The Non-24 patient in the upper right panel has a τ of 24.3 hours corresponding to a circadian cycle of 80 days (Table 1). In other words, this patient's cycle would be aligned with the external 24-hour day once every 80 days. The bottom left panel shows a Non-24 patient with a τ of 24.5 for a cycle length of 48 days. The larger τ results in a shorter circadian cycle so that the patient in the lower right of the slide with the largest τ of 24.8 has a circadian cycle of 30 days (Table 1).

**Figure 8: Composite of Four Raster Plots (Sleep Data) for Patients with Varying τ Values**




The raster plots in Figure 8, representing the timing of an individual's sleep every day, are shown for four individuals with τ corresponding to those shown in Figure 7. Nighttime sleep and daytime sleep duration data reported in daily sleep diaries are double plotted to assist visually in identifying cyclical patterns. The study days are on the y-axis and the hours of the 24-hour day are on the x-axis. The top line shows day 1 followed by day 2, the second line is day 2 followed by day 3, and this pattern continues. In other words, a sliding 48 hour window is plotted, shifted by 24 hours for each line moving down the y-axis. Nighttime sleep is represented by the blue horizontal bars and daytime sleep is represented by the black horizontal bars. The red stars indicate the acrophase, or peak aMT6s secretion.

The entrained patient in the upper left panel of Figure 8 had a sleep period that is consistent and consolidated at the individual's preferred nighttime sleep period. This is reflected in the blue lines evenly aligned with one another and fitting into a similar time every night and the white spaces reflecting limited sleep during the day. Similarly, the acrophase values are constant.

Note that clock time is shown on the x-axis in the raster plot compared to being on the y-axis in the prior τ plots (Figure 5) and therefore the acrophase points for an entrained individual are displayed vertically rather than horizontally.

In contrast to the entrained individual, the three non-entrained patients have a more irregular pattern of sleep, reflected in the shifting and shorter blue lines of nighttime sleep and the more prevalent and also variable black lines of daytime sleep. As these three patients cycle in and out of synch with day and night, they have distinct sleep patterns reflecting their circadian cycles. When their melatonin rhythms are inverted relative to the 24-hour day/night cycle, they are sleeping more during the day and less at night.

These varying positions of an individual being in phase versus out of phase create a jagged or scalloped pattern compared to the smooth edges of the entrained patient at the upper left for the sleep onset and wake times. The different sleep-wake patterns among the three non-entrained patients reflect the pleiomorphic nature of Non-24. The peak levels of aMT6s are occurring at different points throughout the day. When the aMT6s peaks during the daytime, the patient's circadian sleep drive is at the wrong time of day. When that happens, the patients cannot stay awake throughout the day because of their circadian drive to sleep results in a strong drive for unwanted daytime sleep. This sleep drive, based on their circadian rhythm, causes compulsory sleep during the day regardless of the amount of sleep they had the prior night. When the peak melatonin levels are occurring during normal sleep time, the patients may not have any compulsory daytime sleep.

## 5.2. Non-24 Clinical Response Scale (N24CRS)

The N24CRS measurement addresses the cyclical nature of the symptoms of Non-24 by measuring the worst days of the sleep-wake cycle and assesses the overall impact of these symptoms on the patient's functioning.

There are four components of the N24CRS (Table 6). The first three components are patient reported sleep outcomes that assess the worst periods of daytime and nighttime sleep across an adequate evaluation period along with a measurement of the time of day that patients are sleeping (midpoint of sleep timing). The fourth component, Clinical Global Impression of Change (CGI-C), is an established physician reported measure of global functioning.

The lower quartile of nighttime total sleep time (LQ-nTST), measures the average nighttime sleep during the patient's worst 25% of nights. The upper quartile of daytime total sleep duration (UQ-dTSD), measures the average daytime sleep during the worst 25% of days. Midpoint of Sleep Timing (MoST) measures the timing and consolidation of the patient's sleep. In order to be judged a responder for the N24CRS, patients need to experience improvement thresholds on at least three of these four measures (Table 6). Each individual measure comprising the N24CRS

was also evaluated as individual continuous secondary endpoints in the tasimelteon development program.

### 5.2.1. N24CRS Score

Each of the components of the N24CRS is dichotomized to a specific threshold of improvement so that the patient scores one point if improved and a zero if not improved. These thresholds are represented in Table 6.

**Table 6: N24CRS Score**

| Component | Criteria | Score if Criteria Not Met | Score if Criteria Met |
|---|---|---|---|
| CGI-C | ≤ 2 score | 0 | 1 |
| LQ-nTST | ≥ 45min night sleep improvement | 0 | 1 |
| UQ-dTSD | ≥ 45min daytime sleep reduction | 0 | 1 |
| MoST | ≥ 30min improvement (SD <120min) | 0 | 1 |

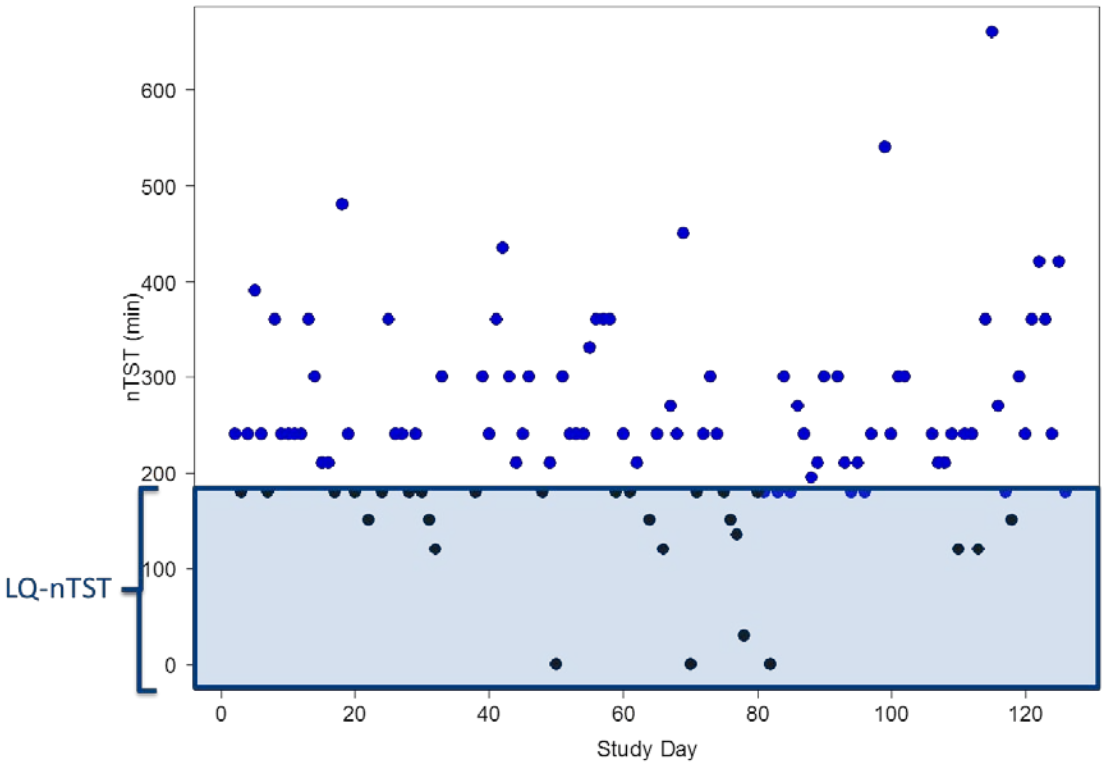
The N24CRS score is the summation across the four subcomponent scores. In order to be considered a responder for the primary efficacy analysis, the patient must show improvement on at least 3 of the four components which translates to a score of 3 or 4.

### 5.2.2. Lower Quartile of Nights of nTST (LQ-nTST)

Patients suffering from Non-24 may have trouble sleeping as a result of their sleep cycle being out of sync with the 24-hour clock. This leads to intervals of poor sleep followed by intervals of good sleep. Therefore, the severity of symptoms associated with Non-24 is best illustrated when isolating the worst nights of sleep and the days with the most daytime sleep. Evaluating the 25% worst nights of sleep, defined as the nights during which patients had the shortest total nighttime sleep, assesses the sleep problem that the patient experiences as a result of this circadian disorder.

To calculate LQ-nTST, all non-missing nighttime total sleep time (nTST) values are ordered from smallest to largest. The first 25% of the records are flagged as belonging to the lower quartile of nighttime total sleep time. The average of these values is calculated and this result is denoted LQ-nTST. This process was performed for the Screening and Double-Masked Phases of both SET and RESET.

**Figure 9: Lower Quartile of Nighttime Total Sleep Time (LQ-nTST)**




The total sleep time reported for a patient is shown in Figure 9. The y-axis is the total sleep per night in minutes and the x-axis is study day. Each dot represents the total nighttime sleep for that day. The blue shading captures the quartile of days the patient had the least nighttime sleep.

### 5.2.3. Upper Quartile of Days of dTSD (UQ-dTSD)

Patients suffering from Non-24 have a propensity to sleep during the day when their sleep cycle is out of sync with a 24-hour clock. In contrast, they may have very little or no daytime sleep when their circadian rhythms are aligned with the 24-hour day. In order to measure the effect of this dynamic circadian disorder on compulsory daytime sleep a robust assessment for measuring the worst of the daytime sleep, the 25% worst days was calculated in a similar fashion as for LQ-nTST. The 25% worst days are defined as the 25% of days with the most total daytime sleep duration.

To calculate UQ-dTSD all non-missing values of daytime total sleep durations are summed for a given day and then these daily summations are rank ordered from largest to smallest (Note: days for which an individual reported no daytime sleep are recorded as zero). The first 25% of the records are flagged as belonging to the upper quartile of daytime total sleep duration. The

average of these values is calculated and this result is denoted UQ-dTSD. This process is performed for the Screening and Double-Masked Phases of both SET and RESET.

**Figure 10: Upper Quartile of Daytime Total Sleep Duration (UQ-dTSD)**

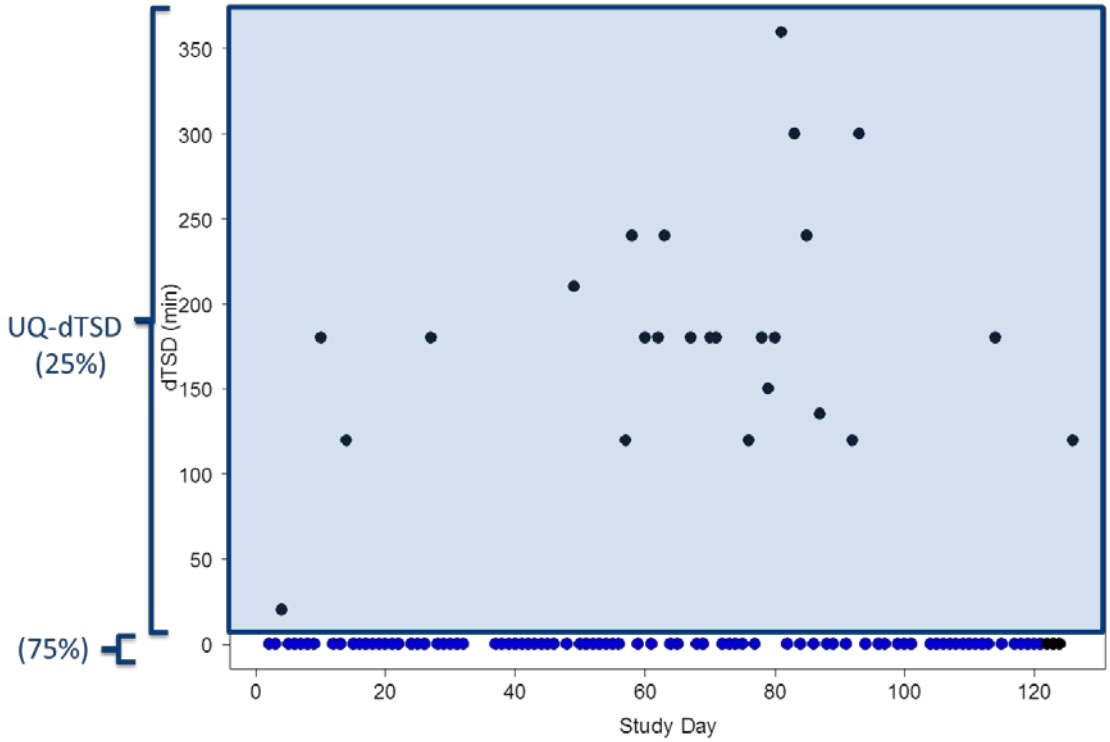


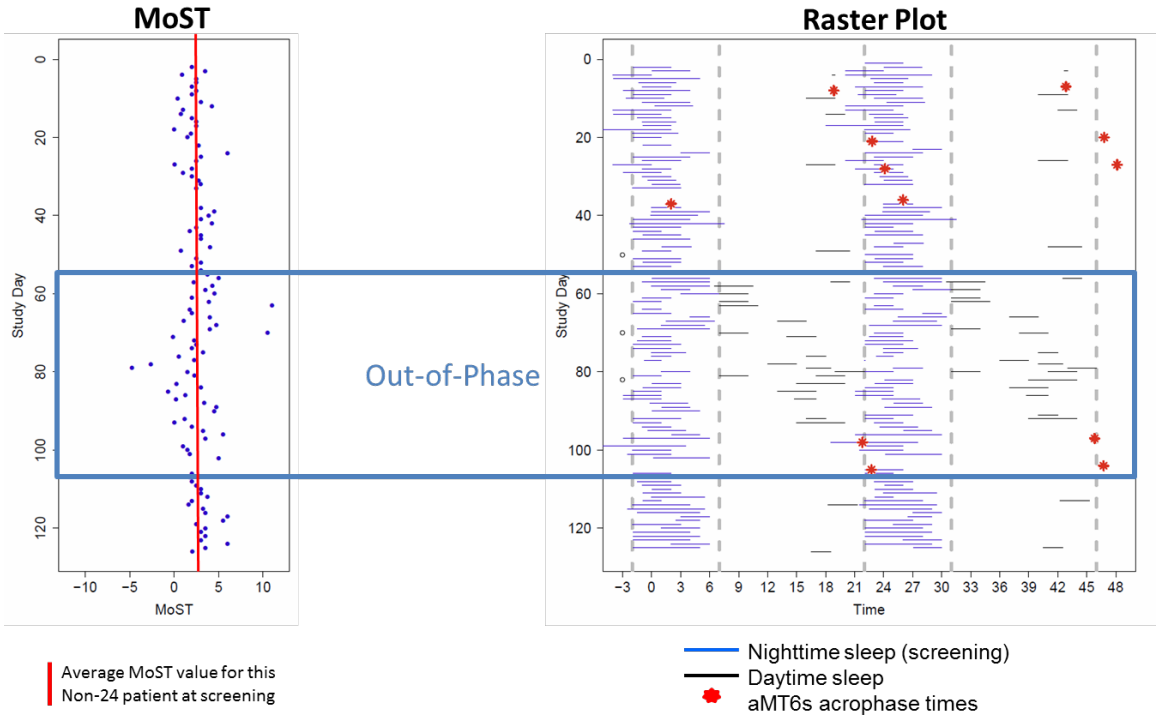

Figure 10 shows the total daytime sleep duration reported for a patient. Even though this patient is able to avoid daytime sleep 75% of days, during the other 25% of days, the average daytime sleep is 3 hours with a maximum of 6 hours which represents a dramatic disruption of daytime wakefulness.

### 5.2.4. Midpoint of Sleep Timing (MoST)

Circadian rhythm disorders, including Non-24, are characterized by a timing misalignment of the circadian rhythms to the 24-hour light-dark cycle. While LQ-nTST and UQ-dTSD measure daytime and nighttime sleep separately, MoST measures the average weighted midpoint of sleep, reflecting both the timing and consolidation of sleep over a 24-hour period. The midpoint of sleep timing over a 24-hour period (adjusted to be relative from -12 hours before bedtime until +12 hours after bedtime) was calculated for each day. The first step in calculating the midpoint is to first calculate the midpoint and weight, i.e. relative duration, for each sleep episode. The total 24-hour sleep time is the summation of all sleep episodes in this 24-hour period. Each of the individual sleep episodes is then assigned a weight relative to the fraction of the total 24-hours of sleep that it contains.

An individual that sleeps at their desired time for 7-8 hours and does not have any daytime sleep has a MoST value between 3.5-4.0. If, however, the individual had a late afternoon sleep episode then MoST would be shifted to a smaller number. To expand on this example, assume an individual with a target bedtime of 10:30PM went to sleep at 10:30PM and woke up at 6:30AM (with a self-reported total sleep time of 5 hours). Assume they had a sleep episode during the day at 8:05 PM that lasted 2 hours and 5 minutes. The mid-point of sleep timing (MoST) for that day would be 1.96 (relative to the target bedtime). This individual had a late afternoon or night sleep episode which pulls the midpoint down to 1.96. Alternatively, if an individual had much less nighttime sleep and suffers from large daytime sleep episodes in the morning then this would potentially lead to a bigger number than 3.5 to 4. This algorithm dynamically takes into account the information from both the nighttime sleep as well as the daytime sleeping. Additionally, because the weighted sleep episodes are divided by the total number of sleep episodes within a 24-hour period the derived midpoint of sleep timing will be pushed to 0 (and away from the optimal value of 3.5-4.0) as an individual's sleep becomes more fragmented. An improvement in MoST is defined as an increase in the MoST value from baseline.

**Figure 11: Midpoint of Sleep Timing (MoST)**




The daily MoST values for a patient are plotted on the left in Figure 11 and their corresponding raster plot is plotted on the right. Over 120 study days are plotted on the y-axis starting with day 0. In the raster plot on the right you can see that when this individual is in-phase at approximately day 40-55 the patient suffers from little daytime sleep and the majority of their

sleep occurs at night during their pre-defined sleep period. During this time the MoST value is close to 4.

They begin to have reduced nighttime sleep and an increase in daytime sleep and on approximately day 80 when the patient suffers from daytime sleep the MoST values are closer to zero. During these days the MoST values become more variable and experience a shift to the left (towards smaller numbers) when this patient is out of phase.

For the MoST endpoint, the score is averaged for the entire period and compared to baseline to determine the extent of change during treatment. If the timing of an individual's sleep is cycling and expressed as a time relative to their target bedtime (-12 to +12 hours), then this average over a time period will trend toward zero if a patient is sleeping at random (or cyclic) times throughout the study period. An increase in MoST represents an improvement.

### 5.2.5. Clinical Global Impression of Change (CGI-C)

The Clinical Global Impression of Change (CGI-C) is a well established physician reported outcome of overall change in symptoms that reflects the general social, occupational, and health functioning of the patient. CGI-C is a 7 point scale (Table 7). A score of 4 is no change. Scores of 3, 2 and 1 represent increasing levels of improvement, and scores of 5, 6, and 7 demonstrate a worsening.

**Table 7: Clinical Global Impression of Change (CGI-C) Rating Scale**

| Score | Classification |
|---|---|
| 1 | Very much improved |
| 2 | Much improved |
| 3 | Minimally improved |
| 4 | No change |
| 5 | Minimally worse |
| 6 | Much worse |
| 7 | Very much worse |

## 5.3. Entrainment Status is Predictive of Clinical Measures

Entrainment status is highly predictive of the clinical measurements of LQ-nTST, UQ-dTSD and MoST as can be seen in an analysis of entrained versus Non-24 patients during the screening portion of the SET study.

**Table 8: Entrainment Status is Predictive of Clinical Measures**

| Clinical Endpoint | Entrained[a] (n=57) | Non-Entrained[a] (n=121) | Delta | p-value |
|---|---|---|---|---|
| LQ-nTST | 4.38 hrs | 3.25 hrs | -1.13 hrs | <0.0001 |
| UQ-dTSD | 1.34 hrs | 2.41 hrs | 1.07 hrs | <0.0001 |
| MoST | 3.51 hrs | 2.79 hrs | -0.72 hrs | <0.0001 |

[a] These data are from the screening phase of the SET study for 178 patients who had both entrainment status and clinical data.

As demonstrated in Table 8, LQ-nTST, UQ-dTSD, and MoST measures are highly specific to Non-24. Non-24 patients experience an average of one hour less sleep during their worst 25% of nights and similarly an hour more daytime sleep during their worst 25% of days compared to their entrained counterparts. As discussed earlier, a healthy individual with consolidated sleep at the right time should have a MoST of around 3.5-4 (hours). Entrained individuals do in fact have an average MoST score of 3.5 hours. Non-Entrained individuals have an average MoST score of roughly 2.8 hours. The clinical endpoints are highly specific to individuals suffering from Non-24 and therefore they serve as specific and meaningful clinical endpoints for the study of potential treatments of Non-24.

# 6. TASIMELTEON EFFICACY

The effectiveness of tasimelteon as a circadian regulator in the treatment of Non-24-Hour Disorder in totally blind individuals was established in two randomized double-masked, placebo-controlled, multicenter, parallel-group trials SET and RESET. Tasimelteon's efficacy as a circadian regulator was supported by the placebo-controlled study VP-VEC-162-2101 in healthy volunteers.

## 6.1. SET Study

### 6.1.1. Study Design, SET

The SET study demonstrated that tasimelteon entrains circadian rhythms in the Master clock located in the SCN and that patients receive clinically meaningful benefit in measures of the sleep-wake cycle and global functioning. The study was a multicenter, randomized, double-masked, placebo-controlled, parallel study designed to evaluate the efficacy and safety of tasimelteon 20 mg versus placebo in patients suffering from Non-24. Eighty-four patients (tasimelteon 42; placebo 42) were randomized to receive tasimelteon (20 mg/day) or placebo.

The study patient inclusion criteria were the following:

1. Totally blind patients with no reported light perception
2. A sleep-wake complaint as assessed by the Sleep-Wake-Questionnaire
3. $\tau \geq 24.25$ hours (95% CI 24.1 – 24.9)

Key study exclusion criteria were:

1. BMI < 18 or > 33 $kg/m^2$
2. Other Sleep or Psychiatric Disorders
3. Medication that could interfere with the evaluation of Circadian Rhythms
4. Age < 18 or >75

The study was conducted at 33 investigative sites in the US (27 sites) and Germany (6 sites). The study included a Screening Phase, a Double-Masked Phase, followed by an Open-Label Extension Phase. Non-24 patients with $\tau > 24.0$ hrs but outside the inclusion criteria limits were given the option to participate in the Open-Label Extension Phase directly from screening. Figure 12 provides a schematic of the study design for the Double-Masked Phase.

The Screening Phase lasted 3 month on average with a range from 6 to 26 weeks, and the Double-Masked Phase was 6 months in duration. The Screening Phase comprised of a screening visit, a circadian period ($\tau$) estimation segment, and a variable-length in-phase transition segment. During the Double-Masked Phase, patients were instructed to take either tasimelteon

20 mg or placebo 1 hour prior to bedtime at approximately the same time every night for 26 weeks. An attempt was made to initiate treatment when a patient's circadian rhythm was in-phase with their preferred timing of nighttime sleep.

The subject selected target sleep-wake schedule and τ information were used to predict when the subject was "in-phase". Precise prediction of this in-phase period was not always possible as discussed in Section 6.4.2 (23).

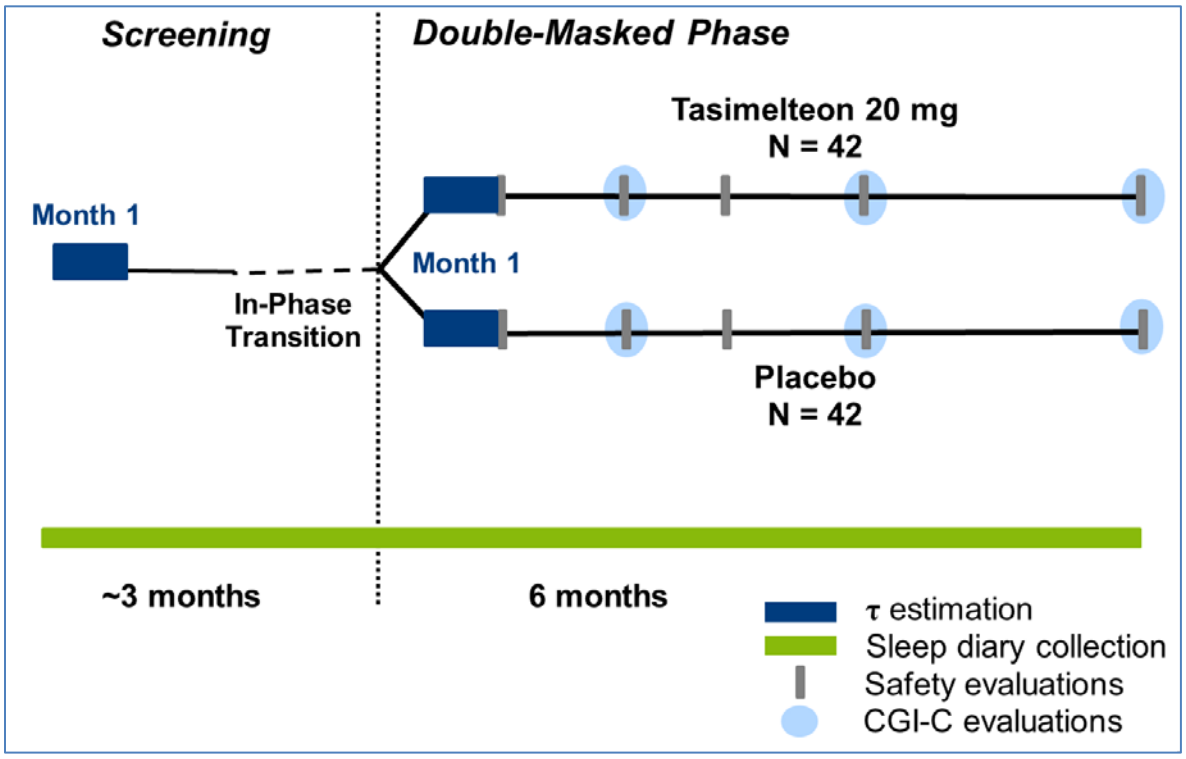
Four types of assessments were performed in the SET Study (Figure 12);

1. circadian period (τ),
2. sleep-wake diaries collected daily via an Interactive Voice Recording System (IVRS)
3. CGI-C, and
4. safety

Circadian period (entrainment status) was assessed during month 1 of the Screening Phase with 4 weekly 48 hour urine collections. Entrainment was assessed early during the Double-Masked Phase beginning at week 2 of treatment and for the following 3 subsequent weeks. The study was designed to assess entrainment status early after treatment initiation in order to minimize missing data, although such early collections may underestimate the entrainment rate effect.

Patients reported their nighttime sleep parameters and daytime sleep parameters for 2.5 circadian cycles or 6 months, whichever was less via an IVRS. Physician's recorded CGI-C at months 2, 4 and 6. Safety assessments including adverse event monitoring, vital signs, electrocardiograms, hematology, chemistry, and urinalysis labs, endocrine testing and suicidality evaluations were conducted at months 1, 2, 3, 4, and 6 (Table 36).

**Figure 12: SET Study Design**




### 6.1.2. SET Study Objectives

The primary objectives of the SET study were:

- To determine the efficacy of tasimelteon in patients with Non-24 as measured by the proportion of entrainment.
- To determine the efficacy of tasimelteon in patients with Non-24 as measured by the proportion of patients with a Clinical Response. Clinical Response was defined as the coincident demonstration of:
  - Entrainment of the aMT6s rhythm and
  - A score of ≥3 on the N24CRS

The success of the trial was based on the rejection of the null hypothesis associated with the proportion of entrainment as measured by aMT6s.

### 6.1.3. Patient Characteristics, SET

#### 6.1.3.1. Patient Disposition

Eighty-four totally blind Non-24 patients were enrolled in the Double Masked Phase out of 391 patients screened (Figure 13). An additional 52 were enrolled in the Open-Label Extension Phase. An equal number of patients were randomized into each treatment group of the Double-Masked Phase: 42 patients in the placebo group and 42 patients in the tasimelteon group. Of these 84 patients who were randomized to study drug, 62 (73.8%) patients completed the Double-Masked phase and 22 (26.2%) patients discontinued early (Figure 14). A total of 55 patients were enrolled in the Open-Label Extension Phase of the study: 52 patients who failed screening for the Double-Masked Phase and 3 patients who completed the Double-Masked Phase.

**Figure 13: Flow Diagram of Patient Disposition (All Patients), SET Study**

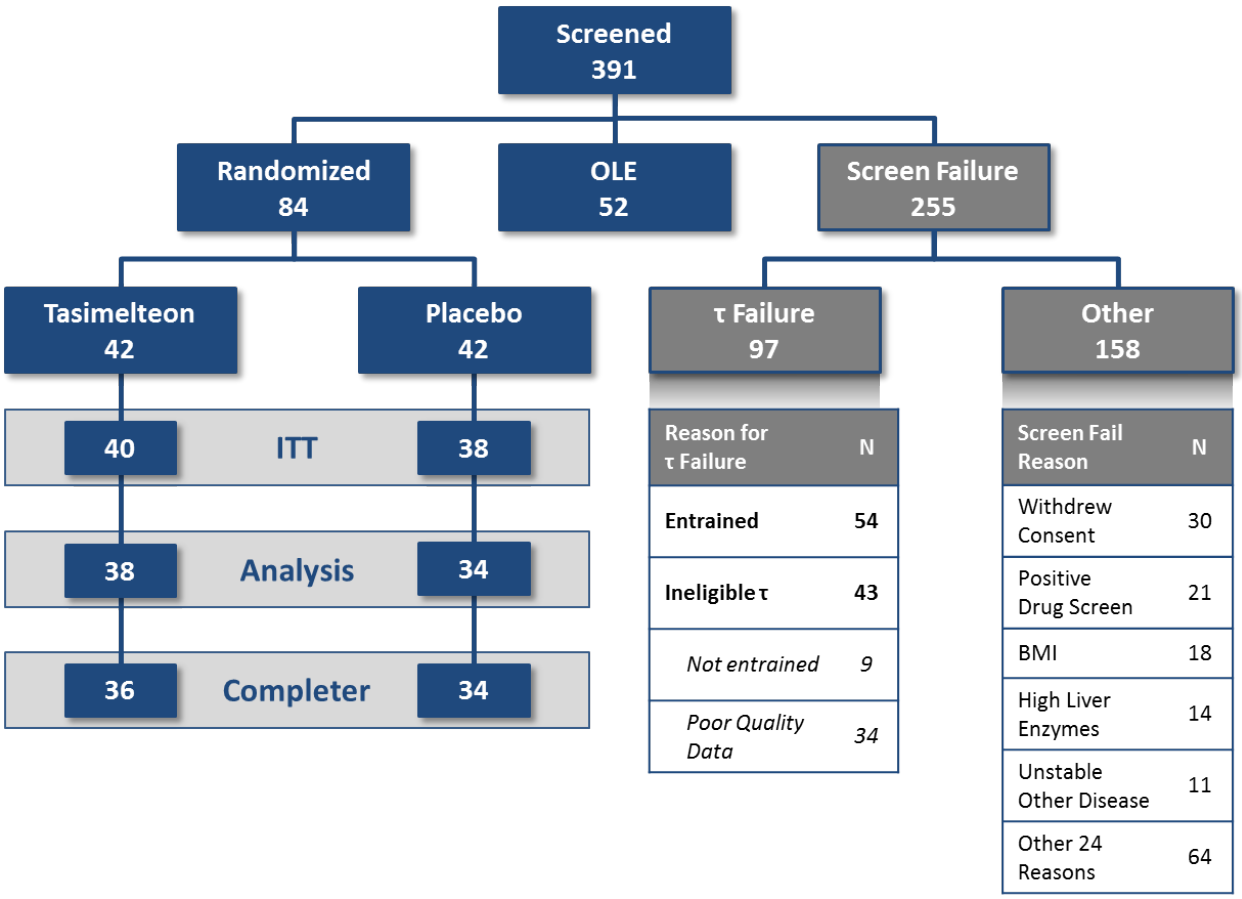
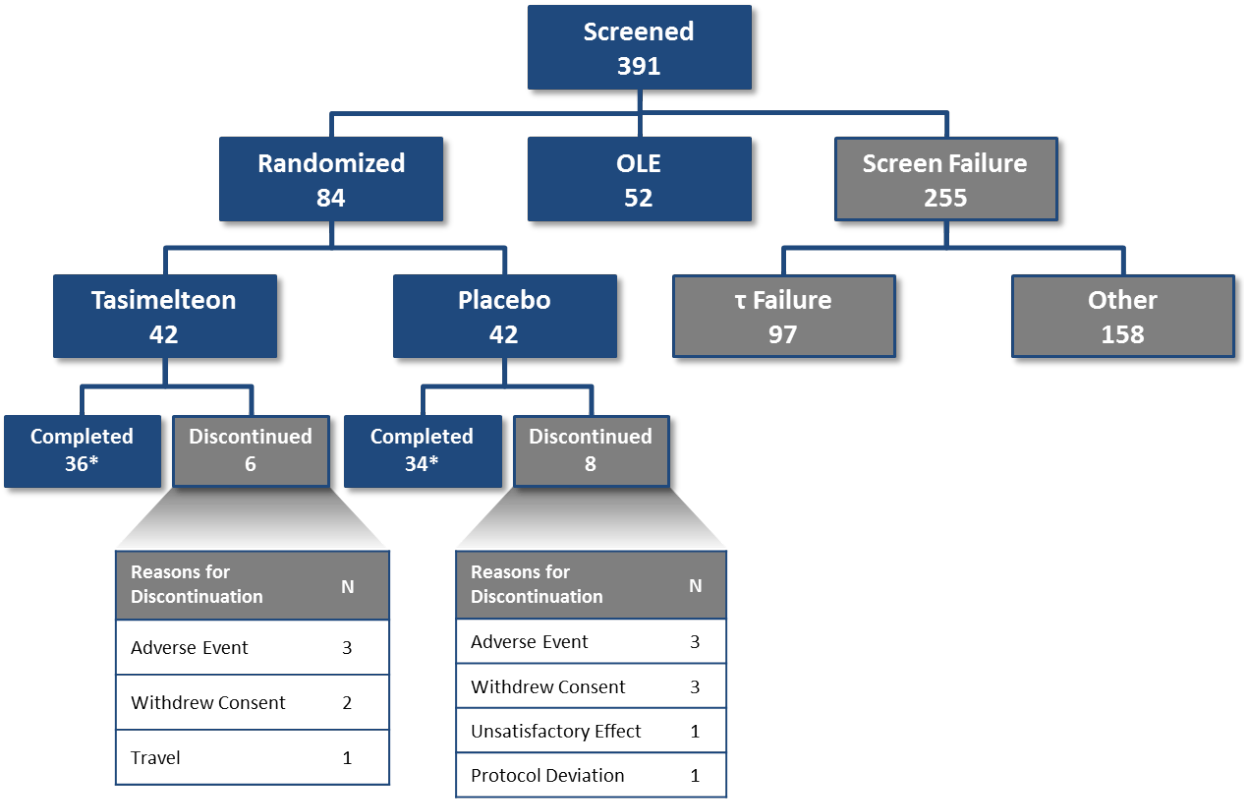


**Figure 14: Reasons for Patient Discontinuations**




| Reasons for Discontinuation | N |
|---|---|
| Adverse Event | 3 |
| Withdrew Consent | 2 |
| Travel | 1 |

| Reasons for Discontinuation | N |
|---|---|
| Adverse Event | 3 |
| Withdrew Consent | 3 |
| Unsatisfactory Effect | 1 |
| Protocol Deviation | 1 |

*Study closed by Sponsor which affected 4 Tasimelteon-treated and 4 placebo-treated patients. All subjects had adequate data collected for the primary and secondary endpoints in the Double-Masked Phase.

### 6.1.3.2. Patient Demographics

Forty-nine males and thirty-five females were randomized in the SET study (Table 9). The mean age was 50.7 years (range of 23 to 74 years). The racial distribution of the patient population was similar to the US population with 83% White and 12% Black or African or African American and the mean BMI was 27.95 kg/m$^2$. There were no significant differences in the demographics between treatment arms.

**Table 9: Demographics -All Randomized Patients**

| | Placebo (N=42) | Tasimelteon 20 mg (N=42) | Total (N=84) |
|---|---|---|---|
| **Age at screening (years)** | | | |
| n | 42 | 42 | 84 |
| Mean (SD) | 50.7 (13.15) | 50.8 (12.63) | 50.7 (12.82) |
| **Age category (n, %)** | | | |
| 18 to 40 years | 9 (21.4) | 10 (23.8) | 19 (22.6) |
| 41 to 65 years | 28 (66.7) | 29 (69.0) | 57 (67.9) |
| >65 years | 5 (11.9) | 3 (7.1) | 8 (9.5) |
| **Gender (n, %)** | | | |
| Male | 25 (59.5) | 24 (57.1) | 49 (58.3) |
| Female | 17 (40.5) | 18 (42.9) | 35 (41.7) |
| **Race (n, %)** | | | |
| American Indian or Alaska native | 1 (2.4) | 0 (0.0) | 1 (1.2) |
| Asian | 0 (0.0) | 1 (2.4) | 1 (1.2) |
| Black or African or African American | 6 (14.3) | 4 (9.5) | 10 (11.9) |
| Native Hawaiian or Other Pacific Islander | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| White | 34 (81.0) | 36 (85.7) | 70 (83.3) |
| Other | 1 (2.4) | 1 (2.4) | 2 (2.4) |
| **Ethnicity (n, %)** | | | |
| Hispanic or Latino | 1 (2.4) | 2 (4.8) | 3 (3.6) |
| Not Hispanic or Latino | 41 (97.6) | 40 (95.2) | 81 (96.4) |
| **Weight at screening (kg)** | | | |
| n | 42 | 42 | 84 |
| Mean (SD) | 78.58 (17.22) | 80.19 (16.31) | 79.39 (16.69) |
| **Body mass index at screening ($kg/m^2$)** | | | |
| n | 42 | 42 | 84 |
| Mean (SD) | 27.73 (3.93) | 28.16 (4.06) | 27.95 (3.98) |

The primary cause of blindness in the population was retinopathy of prematurity followed by ocular trauma, retinoblastoma, and glaucoma (Figure 15). Twenty percent of the blindness was caused by other diseases. There are varied and rare co-morbidities in this patient population.

The baseline efficacy parameter values can be found in (Table 10). There were no notable differences between the placebo and tasimelteon treatment groups in regard to demographic and baseline characteristics in the SET study.

**Figure 15: Causes of Blindness in SET Study Randomized Patients**

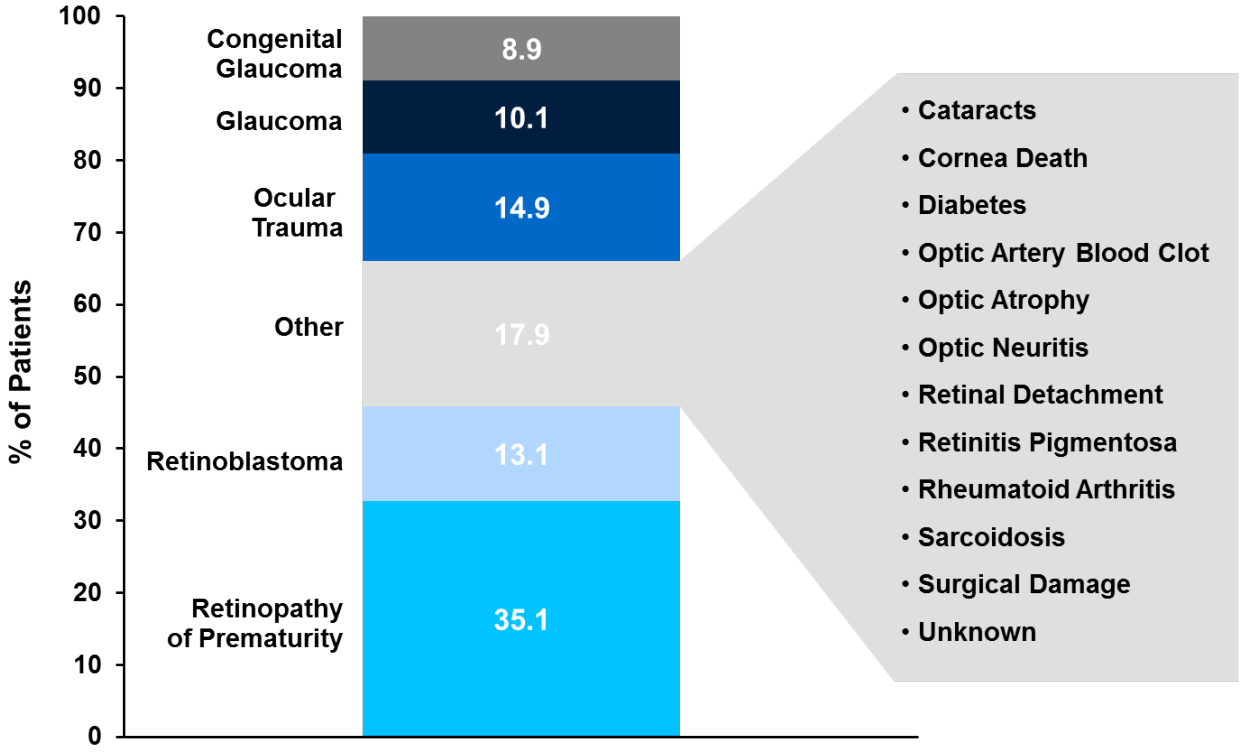



**Table 10: Baseline Values for SET Efficacy Parameters For an Average of 88 Days**

| | Placebo (N=42) | Tasimelteon 20 mg (N=42) | Total (N=84) |
|---|---|---|---|
| **τ (aMT6s) (hours)** | | | |
| Mean (SD) | 24.45 (0.17) | 24.49 (0.16) | 24.47 (0.17) |
| Median | 24.41 | 24.49 | 24.45 |
| **τ (cortisol) (hours)** | | | |
| Mean (SD) | 24.43 (0.32) | 24.48 (0.25) | 24.45 (0.29) |
| Median | 24.42 | 24.47 | 24.46 |
| **Average of LQ-nTST (hours)** | | | |
| Mean (SD) | 3.25 (1.61) | 3.25 (1.19) | 3.25 (1.41) |
| Median | 2.98 | 3.38 | 3.09 |
| **Average of UQ-dTSD (hours)** | | | |
| Mean (SD) | 2.53 (1.71) | 2.29 (1.66) | 2.41 (1.68) |
| Median | 2.10 | 2.01 | 2.07 |
| **Average nTST (hours)** | | | |
| Mean (SD) | 5.42 (1.27) | 5.24 (1.04) | 5.33 (1.16) |
| Median | 5.15 | 5.16 | 5.15 |
| **Average dTSD (hours)** | | | |
| Mean (SD) | 0.97 (0.74) | 0.86 (0.77) | 0.92 (0.76) |
| Median | 0.77 | 0.65 | 0.72 |

### 6.1.4. Key Secondary Efficacy Objectives

The key secondary efficacy objectives of this study were the following:

- To determine the efficacy of tasimelteon in patients with Non-24 as measured by the proportion of entrainment as assessed by urinary cortisol.
- To determine the efficacy of tasimelteon in improving subjective nighttime total sleep time (nTST) in patients with Non-24, as assessed by the change from screening in the average of LQ-nTST;
- To determine the efficacy of tasimelteon in reducing subjective daytime total sleep duration (dTSD) in patients with Non-24, as assessed by the change from screening in the average of UQ-dTSD;
- To determine the efficacy of tasimelteon in patients with Non-24 as measured by the change from the screening in MoST;
- To determine the efficacy of tasimelteon to treat Non-24, as assessed by the CGI-C.

**Table 11: Timing of SET Study Assessments**

| Endpoint | Target of Assessment | Time of Assessment |
|---|---|---|
| Entrainment (aMT6s) | Circadian rhythm | Month 1 |
| Entrainment (cortisol) | Circadian rhythm | Month 1 |
| LQ-nTST | Nighttime sleep, 25% worst | 6 months, daily |
| UQ-dTST | Daytime sleep, 25% worst | 6 months, daily |
| MoST | Timing of sleep | 6 months, daily |
| CGI-C | Global Functioning | Months 4 and 6 |

### 6.1.5. Statistical Methods

A Statistical Analysis Plan was finalized prior to database lock and before any statistical analysis was performed, according to pre-specified criteria. The success of the trial was based on the rejection of the null hypotheses associated with the proportion of entrainment as measured by aMT6s.

The Barnard's exact test was used to test the null hypothesis in the ITT population. If the primary null hypothesis was rejected at an alpha level of 0.05, then the step-down primary null hypothesis would be tested at an alpha level of 0.05 to assess the efficacy of tasimelteon versus placebo as measured by the Clinical Response rate. The Clinical Response rate would be summarized and analyzed in the analysis population in the same manner of the primary endpoint.

In addition to the randomization phase of SET (month 1), $\tau$ was also assessed during the tasimelteon run-in-phase of RESET (month 7). The entrainment status from the open-label run-in phase of RESET was pre-specified for the step-down Clinical Response and secondary analyses and was relevant only for those individuals that were on tasimelteon during the randomization phase of SET. The measures of the N24CRS were derived from the SET randomization phase.

Data were summarized by treatment group (and by visit and study endpoint when applicable), with respect to demographic and baseline characteristics, efficacy variables, and safety variables. Summary statistics included the mean, N, standard deviation (SD), median, minimum, and maximum values for continuous variables, and frequencies and percentages for categorical variables.

No adjustment for multiplicity was planned for secondary endpoints. Statistical analyses were performed using two-sided tests. A 0.05 significance level was used in all tests of treatment differences. Tests for interaction utilized a 0.10 statistical significance level.

Unless otherwise noted, the baseline value for the Double-Masked Phase was defined as the last non-missing measurement obtained prior to the first dose of study drug, and the study endpoint value was defined as the last measurement obtained within 3 days after the last dose from the Double-Masked to the End of Study Visit in each of the Double-Masked Phase.

When the effect of treatment site was assessed in the analysis of covariance (ANCOVA), treatment sites were combined in order to ensure that all sites (or pooled sites, as necessary) contained a minimum of 6 patients with at least 2 patients per treatment group. If a site had less than 6 patients overall or less than 2 patients in any treatment group, it was pooled with another small site until the resulting pooled site has reached the threshold. For the purpose of efficacy analyses, a small site in this study was defined as a site with less than 2 patients in 1 or more

treatment groups or sites with fewer than 6 patients in total. Small sites were then pooled to form pseudo-sites so that each site included at least 2 patients per treatment group and at least 6 patients overall.

#### 6.1.5.1. Analysis Population Definitions

The following analysis populations were defined for this study:

**Intent-to-Treat (ITT) Population:** The ITT Population included all patients randomized into the study that had τ estimated post-randomization (N=78).

**Intent-to-Treat* (ITT*) Population:** The ITT* Population included all patients randomized into the study who had at least one dose of treatment and who had at least one efficacy assessment (N=84).

**Analysis Population:** The Analysis Population included all patients in the ITT population that had at least 70% of 1 circadian cycle of nTST data reported during each screening and post-randomization (N=72).

The number of non-missing days of nTST data during each of screening and post-randomization had to be at least equal to the number of days that made up 70% of 1 circadian cycle.

**Safety Population:** The Safety Population included all patients randomized into the study who received at least 1 dose of study drug (N=84).

The ITT population was predefined in the Statistical Analysis Plan and utilized for the primary endpoint of entrainment and the secondary cortisol entrainment endpoint. A post-hoc analysis using the ITT* population was requested by the FDA as a sensitivity analysis during the pre-NDA meeting. The Analysis Population was predefined in the Statistical Analysis Plan and used for analysis of all other endpoints including the Clinical Response primary endpoint and all other efficacy analyses. Safety summaries were based on the Safety Population. Patient characteristics were presented for all patients randomized.

#### 6.1.5.2. How Missing Data Was Handled

Six (6) patients did not have a τ estimated during the Double-Masked Phase due to early discontinuation or insufficient urine collections for τ estimation. These 6 patients were excluded from the analysis of entrainment in the protocol defined ITT population. For the entrainment analysis in the FDA requested ITT* population, these 6 patients were automatically excluded because of the missing entrainment information; no imputation for entrainment was performed.

All other analyses were conducted including patients with non-missing values in each of the endpoints being analyzed. All missing data were excluded at the analysis level and no imputation was conducted.

The amount of missing nighttime sleep and daytime sleep was minimal. For the all patients that participated in the Double-masked Phase approximately 9 % of data for the sleep questionnaires was missing for both treatment arms. In the analysis population, 6.4% of sleep questionnaire data were missing in the placebo arm and approximately 8.4% were missing in the tasimelteon arm.

### 6.1.6. Tasimelteon Succeeded in Both the Primary Endpoints for the SET Study

Tasimelteon achieved the primary efficacy endpoints in the SET study;

- Entrainment of circadian rhythms as measured by aMT6s, and
- Clinical Response defined as demonstration of entrainment of aMT6s and a score ≥3 on the N24CRS.

The primary endpoints were both categorical endpoints. Both primary endpoints were achieved for SET, demonstrating that tasimelteon treated patients achieved entrainment (p= 0.0171) and Clinical Response (p= 0.0028) at higher rates as compared to placebo (Table 12).

Twenty percent (8/40) of tasimelteon treated patients were entrained as early as week 2, compared to just 2.6% (1/38) in placebo treated patients. The 20% entrainment rate with tasimelteon is expected to significantly underestimate the true rate of entrainment given the early evaluation beginning at week 2 after treatment. While efforts were made to initiate treatment during an aligned portion of the circadian phase (in-phase), for some patients this did not occur and therefore entrainment could only be achieved after treatment for about one circadian period length (average of 40-80 days). A subsequent analysis of entrainment rate for those patients with later evaluation at Month 7 suggests a rate of approximately 59% (10/17) (Figure 17). This is also consistent with an entrainment rate of 50% (24/48) obtained among patients that were screened for inclusion in the RESET study (Figure 20).

The second primary endpoint was Clinical Response defined as a patient with both entrained melatonin rhythm and a score of at least 3 in the N24CRS scale. As N24CRS was calculated from the totality of 2.5 circadian cycles up to180 days of observation, entrainment data also used the totality of available entrainment data from months 1 and 7 when available (Figure 17). Based on these data 23.7% (9/38) tasimelteon treated patients were classified as Clinical Responders as compared to 0.0% (0/34) for placebo (Table 12).

A number of sensitivity analyses for this primary endpoint were conducted. Regardless of utilization of entrainment data from Month 1 or 7 the Clinical Response result remains significant. Similarly, a sensitivity analysis using entrainment plus N24CRS cutoff value of 2 also supports the same conclusion of tasimelteon efficacy (Table 13). Analyses based on a N24CRS scale at cut-off values of ≥2 or ≥3 regardless of entrainment status as well as an analysis of N24CRS as a continuous variable (tasimelteon: 1.77 and placebo: 0.67 with p-value =

0.0004) all support the efficacy of tasimelteon (Table 13, Figure 16, and Figure 18). In summary all sensitivity analyses support the conclusions of the primary endpoints.

**Table 12: SET Study Primary Endpoint Results**

| Statistic | Placebo (%) | Tasimelteon 20 mg (%) | P-value[1] | P-Value[2] |
|---|---|---|---|---|
| **Entrainment rate (month 1)** | 1/38 (2.6) | 8/40 (20.0) | 0.0171 | 0.0291 |
| **Entrainment[3] and N24CRS ≥3** | 0/34 (0.0) | 9/38 (23.7) | 0.0028 | 0.0025 |

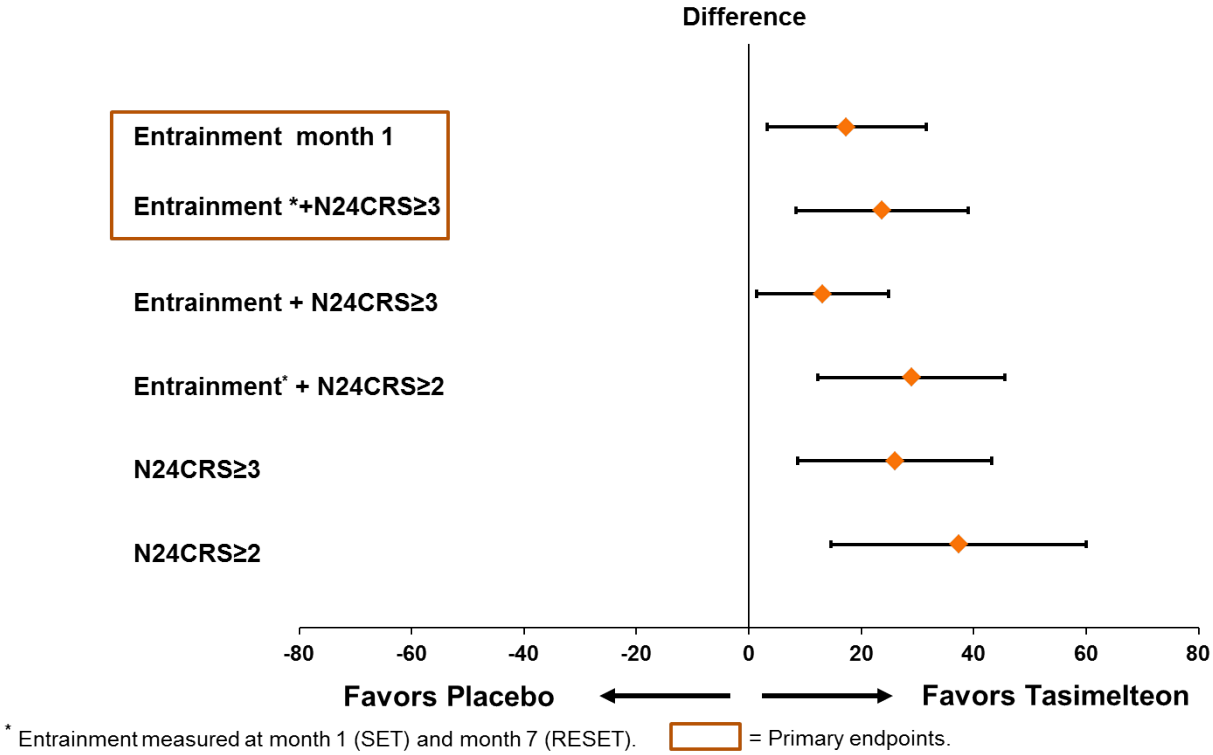
[1] P-value was based on Barnard's Exact Test, two-sided.
[2] P-value was based on Fisher's Exact Test, two-sided.
[3] Entrainment defined as a post-baseline τ value <24.1 and 95% CI that included 24.0. Results based on month 1 or 7.

**Table 13: SET Study Clinical Response Sensitivity Analyses**

| Statistic | Placebo n (%) (N=34) | Tasimelteon 20 mg n (%) (N=38) | P-value[1] |
|---|---|---|---|
| **Entrainment (month 1) and N24CRS ≥3[2]** | 0 (0.0) | 5 (13.2) | 0.0286 |
| **Entrainment (month 1 and month 7)[3] and N24CRS ≥2[2]** | 0(0.0) | 11(28.9) | 0.0006 |
| **N24CRS ≥3[2]** | 1 (2.9) | 11 (28.9) | 0.0031 |
| **N24CRS ≥2[2]** | 7 (20.6) | 22 (57.9) | 0.0014 |

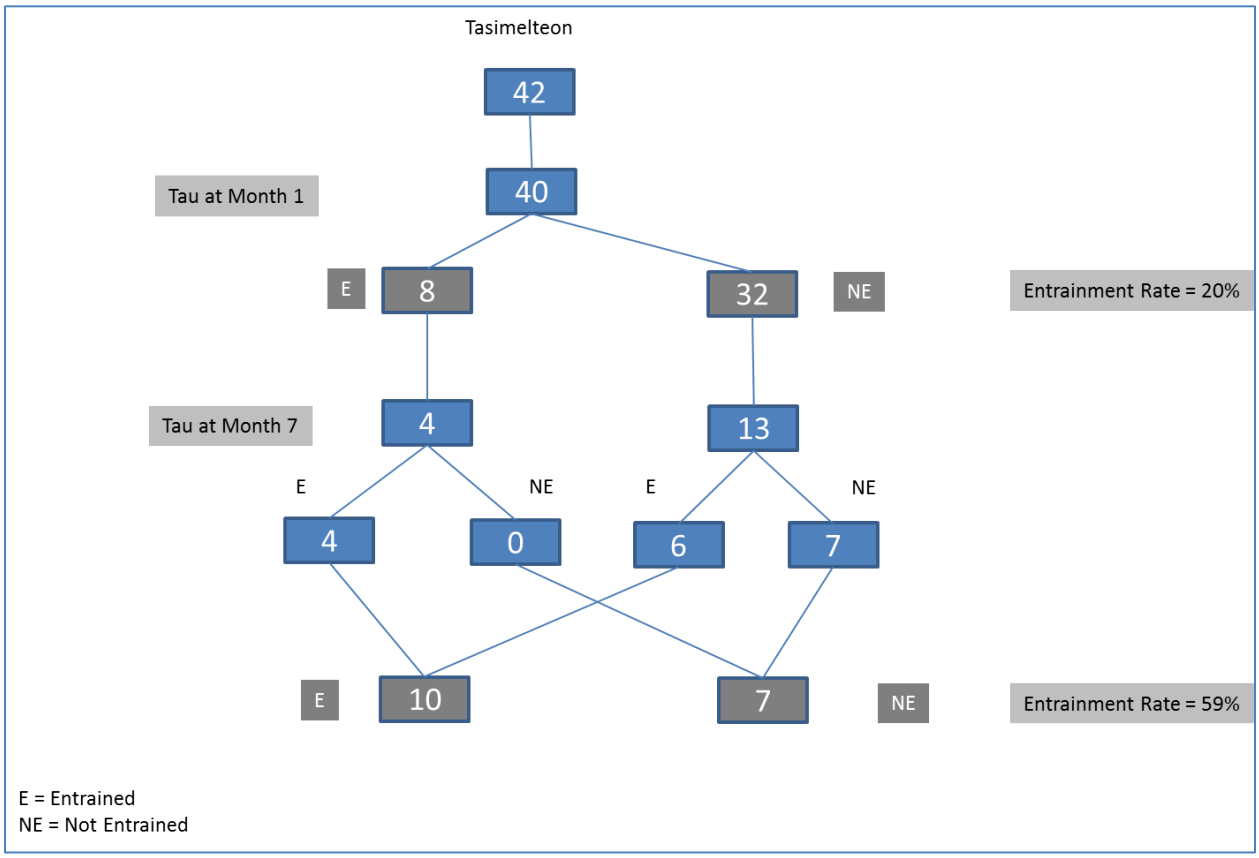
[1] P-value was based on Barnard's Exact Test, two-sided.
[2] Non-24 Clinical Response Scale was a 4-item scale that included LQ-nTST, UQ-dTSD, MoST, and CGI-C assessments. Results based on the Analysis population
[3] Entrainment based on the first month or seventh month (SET Double-Masked Phase or RESET Run-in Phase respectively).

**Figure 16: Forest Plot of SET Primary Endpoints and Sensitivity Analyses**




* Entrainment measured at month 1 (SET) and month 7 (RESET). = Primary endpoints.

**Figure 17: Disposition of Patients in SET Tasimelteon Arm for Month 1 and Month 7**




Further analysis was conducted that assessed entrainment during month 1 and again at month 7 in 17 patients that received tasimelteon during the randomized phase of the SET study and who continued into the run-in phase of RESET (Figure 17). Of these patients, 10/17 (59%) patients entrained (four patients entrained at month 1 plus 6 additional patients that entrained at month 7, Table 14). An additional four patients that entrained at Month 1 were not assessed at month 7 and are not included in the analysis. These results demonstrate that if an adequate trial of treatment is provided that tasimelteon will entrain the Master clock in approximately 59% of patients treated for 7 months.

**Table 14: Entrainment Rate for Tasimelteon after Month 1 and Month 7**

| **Statistic** | **Month 1**[1] (N=40) | **Month 7**[2] (N=17) |
|---|---|---|
| Entrainment | 8/40 (20%) | 10/17 (59%) |

[1] Data from month 1(SET Double-Masked Phase).
[2] Data from month 1 (SET Double-Masked Phase) and month 7 (RESET Run-in Phase).

### 6.1.7. Key Secondary Endpoints

#### 6.1.7.1. Tasimelteon Entrains The Master clock as Measured by Cortisol

Among the entrained patients, inspection of cortisol rhythms confirmed that both melatonin and cortisol rhythms are entrained by tasimelteon suggesting an action at the site of the Master clock in the SCN (Table 15). The proportion of Non-24 patients who were entrained (cortisol) after tasimelteon treatment during the Double-Masked Phase was statistically significantly greater than the proportion of Non-24 patients who were entrained after placebo treatment (difference = 14.9%; p = 0.0313). Entrainment of melatonin and cortisol, two separate endocrine hormones synthesized by two separate glands, the pineal and adrenal, that both are regulated by the Master clock are corroborating evidence that tasimelteon entrains the Master clock.

**Table 15: Tasimelteon Entrains Cortisol Circadian Rhythms**

| Statistic | Placebo | Tasimelteon 20 mg | Treatment Difference (Tasimelteon minus Placebo) | P-value[1] |
|---|---|---|---|---|
| Entrainment (cortisol), n /N (%) | 1/38 (2.6) | 7/40 (17.5) | 14.9 | 0.0313 |

[1] P-value was based on Barnard's Exact Test, two-sided

#### 6.1.7.2. Tasimelteon Improves Nighttime Sleep, Daytime Sleep, Timing of Sleep and CGI-C

**Tasimelteon Improved Nighttime and Daytime Sleep Measures**

Patient reported nighttime and daytime sleep diaries were collected for an average of 88 days and 133 days during the Screening and Double-Masked Phases respectively. Tasimelteon treated patients had improvements in LQ-nTST of nearly 1 hour/night (56.8 minutes) while the placebo improvement was 17.1 minutes/night, with the between treatment improvement in tasimelteon equal to 39.7 minutes (p =0.0055) (Table 16). A 1 hour/night improvement in nighttime sleep is highly clinically meaningful and represents a 31% increase from the baseline LQ-nTST value of 3.25 hours.

**Table 16: Summary of Key Secondary Clinical Response Endpoints-SET Study (Analysis Population)**

| Statistic | Placebo N=34 | Tasimelteon 20 mg N=38 | Treatment Difference (Tasimelteon minus Placebo) | P-value |
|---|---|---|---|---|
| LQ-nTST (LS mean minutes)[1] | 17.08 | 56.80 | 39.71 | 0.0055 |
| UQ-dTSD (LS mean minutes) [1] | -17.87 | -46.48 | -28.61 | 0.0050 |
| MoST (LS mean minutes) [1] | 14.48 | 35.00 | 20.52 | 0.0123 |
| CGI-C (LS mean)[2,3] | 3.4 | 2.6 | -0.8 | 0.0093 |

[1] P-value was based on analysis of co-variance model.
[2] P-value was based on analysis of variance model.
[,3] The placebo arm had N=33 and tasimelteon arm had N=36
CGI-C = Clinical Global Impression-Change; CI = confidence interval; LQ-nTST = lower quartile of subjective nighttime total sleep time; LS mean = least-squares mean; MoST = midpoint of sleep timing;

Treatment with tasimelteon resulted in a greater reduction in daytime sleep duration compared to placebo. The LS mean change from baseline in UQ-dTSD after tasimelteon treatment during the Double-Masked Phase was significantly greater than that after placebo treatment (LS mean difference = -0.48 hours (-28.61minutes); p = 0.0050 [ANCOVA]) (Table 16). Patients on tasimelteon slept 47 minutes less during the day for their worst 25% of days with excessive daytime sleeping. This decrease of 0.78 hours/day during the worst days is clinically meaningful and represents an average 33 % change from the baseline value 2.4 hours/day of UQ-dTSD at baseline (Table 10).

A sensitivity analysis of effects on total nighttime sleep and daytime sleep is consistent with the effects described in the pre-specified primary and secondary analysis. In the ITT population tasimelteon as compared to placebo, significantly improved nighttime total sleep time (nTST) (p=0.028) as well as daytime total sleep duration (dTSD) (p=0.006).

**Clinical Response to Treatment Among Entrained Patients**

An exploratory analysis was performed to assess the magnitude of the clinical response in patients that had entrained circadian rhythms. Responders, patients that had entrained at either Month 1 or Month 7 (Table 17) experienced a 97 minute increase in nighttime sleep and a decrease of 94 minutes of daytime sleep/day as measured by LQ-nTST and UQ-dTSD.

**Table 17: Clinical Response to Tasimelteon Treatment Among Entrained Population**

| SET Study: Analysis Population | Responder (Entrained) N=13[1] | Placebo N=34 | Difference | p-value |
|---|---|---|---|---|
| LQ-nTST | 97.69 | 15.34 | 82.35 | 0.0001 |
| UQ-dTSD | -94.58 | -20.94 | -73.63 | <0.0001 |

[1] Eight subjects entrained at month 1, six additional subjects entrained by month 7, for a total of 14 subjects in the tasimelteon arm of SET that entrained at either month 1 or month 7. One of the 14 subjects withdrew and is not included in the analysis population because they did not have 70% of one circadian cycle of data.

### 6.1.7.3. Tasimelteon Improves the Timing of Sleep

Compared to placebo, treatment with tasimelteon resulted in a greater increase in midpoint of sleep timing. The mean MoST value at baseline was similar between placebo and tasimelteon (2.61 and 2.85 respectively). The LS mean change from baseline in MoST after tasimelteon treatment during the Double-Masked Phase was statistically significantly greater than the LS mean change from baseline in MoST after placebo treatment (LS mean difference = 0.34 hours (20.52 minutes); p = 0.0123 [ANCOVA] Table 16: Summary of Key Secondary Clinical Response Endpoints-SET Study (Analysis Population). This is further evidence that tasimelteon treated patients shifted more of their sleep into nighttime and reduced their daytime sleep, resulting in an increased MoST score.

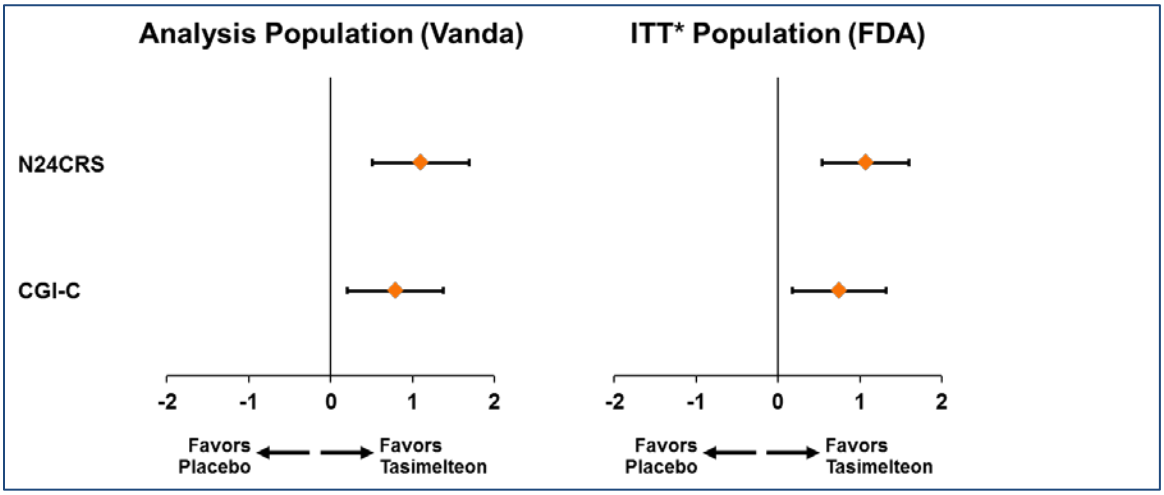
### 6.1.7.4. Tasimelteon Improves Global Functioning as Measured by Clinical Global Impression of Change

The CGI-C scores ranges from 1 (very much improved) to 7 (very much worse). The average post-randomization score was obtained for each patient by averaging the last 2 scheduled assessments (Month 4 and Month 6).Compared to placebo, treatment with tasimelteon resulted in a greater improvement in post-randomization CGI-C scores. The LS mean CGI-C score after tasimelteon treatment during the Double-Masked Phase was statistically significantly lower than the LS mean CGI-C score after placebo treatment (LS mean difference = -0.8; p = 0.0093 [ANOVA]) (Table 16, Figure 18).

There was a statistically significant difference between tasimelteon and placebo in the proportion of patients with ‘improved’ and ‘not improved’ for the average of CGI-C (dichotomized response) post-randomization scores (p = 0.0326). ‘Improved’ was defined as having the average post-randomization score showing at least minimal improvement (≤ 3), while ‘not improved’ was defined as having the average post-randomization score > 3.

In addition to improvement demonstrated by the average CGI-C scores, higher percentages of patients in the tasimelteon group had CGI-C scores in the categories of 'much improved' and 'very much improved' than in the placebo group at each visit. This treatment difference was statistically significant at Day 112 (p = 0.0163), Day 183 (p = 0.0109), and study endpoint (p = 0.0117). Results were similar during the Open-Label Extension Phase, with the majority (80% on day 56) of patients having CGI-C scores in the categories of 'minimally improved', 'much improved', and 'very much improved' after tasimelteon treatment.

**Figure 18: Forest Plots of N24CRS (Continuous) and CGI-C from the SET Study**




## Clinician and Patient Global Impression of Change in Study 3202

Measures of clinical and patient reported global functioning were assessed in Study 3202, an open-label, multi-center safety study in Non-24 patients who were totally blind conducted in France (Table 43). Global functioning was assessed at Months 2, 4, 6, 8, 10, and 12 using three scales: CGI-C, Patient Global Impression of Change (PGI-C) for nighttime sleep, and PGI-C for daytime sleep. The PGI-C scales are patient reported outcomes for nighttime sleep and daytime sleep are similar to the CGI-C scale. Table 18 summarizes the average post-randomization value for each scale. The average post-randomization score was obtained for each patient by averaging the scores of all visits available at the time of the interim database lock.

The mean (standard deviation [SD]) change from baseline for the CGI-C was 2.26 (0.843) corresponding to "much improved", with a majority (87.8%) of patients showing improvement. The mean (SD) average post-randomization score for PGI-C for nighttime sleep was 2.37 (0.820), with a majority (85.4%) of patients showing improvement. The mean (SD) average post-randomization score for the PGI-C for daytime sleep episodes was 2.76 (1.020), with a majority (68.3%) of patients showing improvement. While these results are not placebo-controlled the

magnitude of change for both the PGI-C and CGI-C are consistent with each other in 3202 and are consistent with the magnitude of change for CGI-C in the SET study.

**Table 18: Summary of Study 3202 (Open-label) Efficacy Evaluation**

| **Category**<br>Statistic | **CGI-C**<br>N=41 | **PGI-C nighttime sleep**<br>N=41 | **PGI-C daytime sleep**<br>N=41 |
|---|---|---|---|
| Mean (SD) | 2.26 (0.843) | 2.37 (0.820) | 2.76 (1.020) |
| **Response** | | | |
| Improved[1] | 36 (87.8) | 35 (85.4) | 28 (68.3) |
| Not Improved | 5 (12.2) | 6 (14.6) | 13 (31.7) |

[1] Very much improved, much improved or minimally improved
CGI-C = Clinical Global Impression of Change; PGI-C = Patient Global Impression of Change

**Patients Entrained with Tasimelteon Treatment Experience Clinically Meaningful Benefit**

Figure 19 represents raster plots of two patients that received tasimelteon during the Double-Masked Phase of the SET study and responded with entrainment of their circadian rhythms and clinically meaningful improvement of their sleep-wake cycle. The raster plots provide a visual of the composite entrainment, nighttime sleep, and daytime sleep assessments over the entirety of the SET study.

The format for the raster plots are similar to those previously described. The first patient has a $\tau$ =24.59 (95% CI: 24.52 - 24.66) and a cyclical sleep latency and early morning awakening problem during screening. Tasimelteon treatment stabilizes his sleep-wake schedule with a significant increase in their LQ-nTST of 2.37 hours from screening and reduction of UQ-dTSD by 3.03 hours (Table 19). The patient is entrained in the Double-Masked Phase, $\tau$ =24.01 (95% CI: 24.00 - 24.02), red stars occur at the same time every week after treatment initiation, and their N24CRS score = 4.

Patient two has a screening $\tau$ =24.58 (95% CI: 24.48 - 24.67). Tasimelteon treatment entrains their circadian rhythms, $\tau$ =24.00 (95% CI: 23.91 - 24.08) and improves overall nighttime sleep and decreases daytime sleep. His daytime sleep was potentially habitual as well as circadian, which may explain why not all of the daytime sleep dissipates in the second patient even with entrainment of aMT6s and improvement in the nighttime sleep. LQ-nTST increases by1.68 hours and UQ-dTSD decreases by 1.3 hours. Their N24CRS score = 3.

**Figure 19: Raster Plots of Two Patients that Responded to Tasimelteon Treatment in the SET Study**

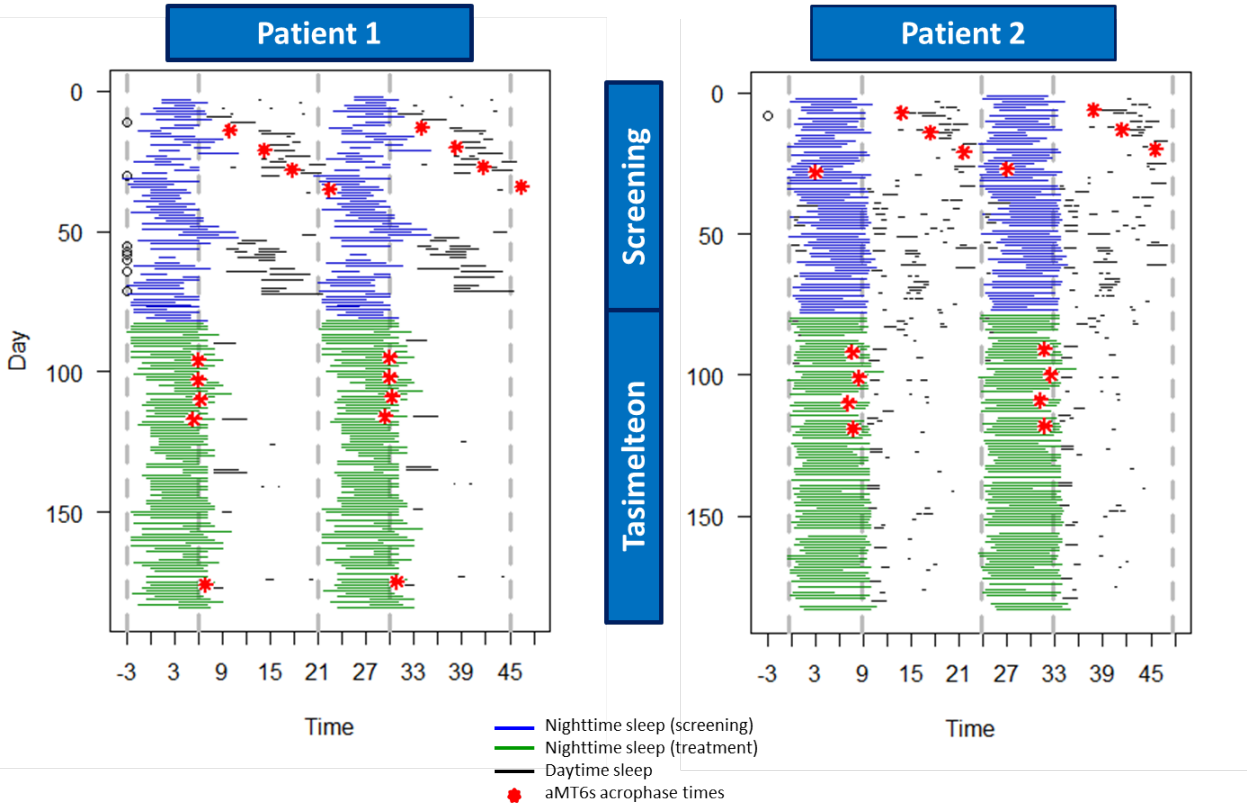



**Table 19: Average LQ-nTST and UQ-dTSD for Patients 1 and 2 in Figure 19**

| | Patient 1 | | Patient 2 | |
|---|---|---|---|---|
| **STUDY Phase** | **LQ-nTST (hours)** | **UQ-dTSD (hours)** | **LQ-nTST (hours)** | **UQ-dTSD (hours)** |
| SET Screening | 1.35 | 3.69 | 4.53 | 2.51 |
| SET Tasimelteon | 3.72 | 0.66 | 6.21 | 1.20 |

### 6.1.8. SET Study Efficacy Conclusions

- Tasimelteon entrained the Master clock to a 24-hour day as measured by aMT6s and cortisol circadian rhythms.
- Tasimelteon had a clinically meaningful improvement as measured by the assessment of clinical response and the Non-24 Clinical Response Scale.
- Tasimelteon demonstrated clinically meaningful improvements across a number of sleep/wake parameters controlled by the Master clock including decreasing the amount of daytime, increasing the amount of nighttime sleep, and optimizing the timing of sleep to a desired time.
- Tasimelteon showed significant improvements over placebo in global functioning.

## 6.2. RESET Study

### 6.2.1. Study Design, RESET

The RESET study was a multicenter, randomized withdrawal, double-masked, placebo-controlled, parallel group study designed to evaluate the long-term maintenance effect and safety of 20 mg of tasimelteon versus placebo in patients with Non-24. The rarity of Non-24 and low awareness among patients and healthcare providers made recruiting for this study extremely difficult. Given the challenges to recruitment the FDA recommended enrolling patients from the SET study in the RESET study at the End of Phase 2 meeting. Every patient who enrolled in RESET had previously been screened in SET, Figure 20. Patients who met the inclusion criteria and who had previously participated in, or were screened for SET, were eligible to participate. The study had 2 phases: a Pre-Randomization Phase (consisting of an Open-label tasimelteon Run-in Phase [~6 weeks] and a $\tau$ Estimation Phase [~ 6 weeks]), and a Randomized Withdrawal Phase (~8 weeks). Please see Figure 8.

**Figure 20: Patient Flow from SET to RESET**

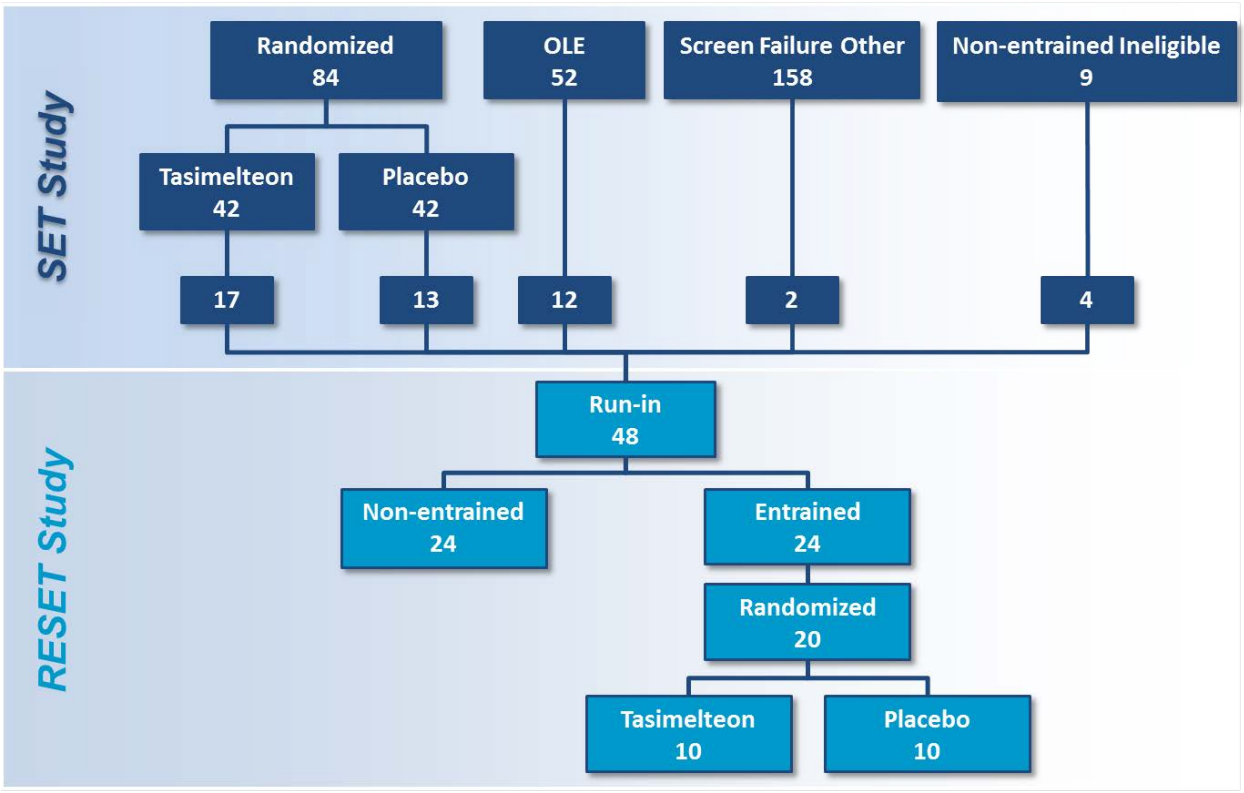
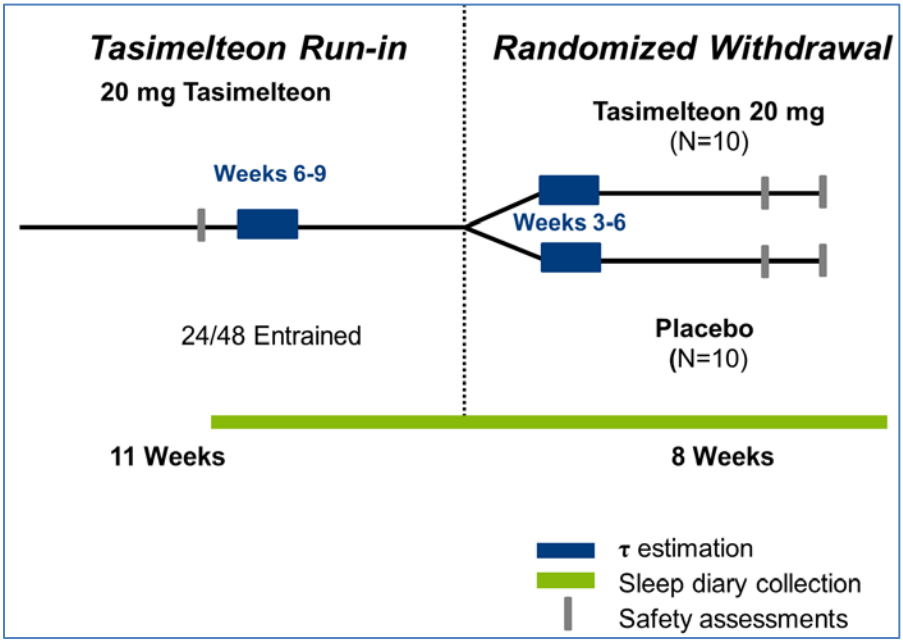



**Figure 21: RESET Study Design**



During the tasimelteon Run-in Phase, all patients who met the eligibility criteria were treated with 20 mg/day of tasimelteon for 6 weeks. The purpose of this phase was to provide an opportunity for every patient, including those who had been randomized to placebo or may not have received any treatment in SET (e.g. came directly from the screening phase), to receive and respond to treatment with tasimelteon. Circadian period ($\tau$) was estimated using the same methodology used in SET. This measurement was used to determine if Non-24 patients had responded to tasimelteon treatment as evidenced by entrainment of their circadian rhythms to a 24-hour day. Urinary cortisol was also analyzed at each time point.

Patients whose aMT6s $\tau$ values indicated entrainment to a 24-hour clock were randomized to receive either placebo or 20 mg tasimelteon once daily for 8 weeks. The maintenance of tasimelteon effect was evaluated during the Randomized Withdrawal Phase.

### 6.2.2. RESET Study Objectives

**Primary Objective**

The primary objective of this study was to demonstrate the maintenance of effect of tasimelteon to entrain circadian rhythms in patients with Non-24 as measured by urinary aMT6s.

**Secondary Objectives**

The key secondary efficacy objectives of this study were the following:

- To demonstrate the maintenance of effect of tasimelteon to entrain circadian rhythms in patients with Non-24 as assessed by urinary cortisol;
- To demonstrate the maintenance of effect of tasimelteon on subjective nTST in patients with Non-24, as assessed by the change from the Run-in Phase in the average nTST;
- To demonstrate the maintenance of effect of tasimelteon on subjective nTST in patients with Non-24 as assessed by the change from the Run-in Phase in the lower quartile of days of nTST (LQ-nTST);
- To demonstrate the maintenance of effect of tasimelteon on subjective daytime total sleep duration (dTSD) in patients with Non-24, as assessed by the change from the Run-in Phase in the average dTSD;
- To demonstrate the maintenance of effect of tasimelteon on subjective dTSD in patients with Non-24, as assessed by the change from the Run-in Phase in the upper quartile of days of dTSD (UQ-dTSD);

- To demonstrate the maintenance of effect of tasimelteon on the midpoint of sleep time (MoST);
- To demonstrate the maintenance of effect of tasimelteon as measured by the proportion of patients with non-entrainment and an average of 30 minutes or greater decrement of nTST compared to the run-in phase;
- To demonstrate the maintenance of effect of tasimelteon to treat Non-24 as measured by the time to relapse with relapse defined as a 45 minute or greater decrement in the weekly average subjective nighttime total sleep time (nTST) compared to the Run-in Phase.

### 6.2.3. Patient Characteristics, RESET

Fifty-eight patients were screened in the RESET study and 48 completed the circadian period assessment during the Run-In phase (Figure 20). During the 6 weeks run-in phase tasimelteon entrained the aMT6s circadian rhythms for 24/48 (50%) of the patients for whom $\tau$ was estimated (Figure 20). Twenty of the patients who were entrained continued into the Double-Masked Phase where 10 were randomized to continue on 20 mg of tasimelteon and 10 were dosed with placebo for 6 weeks. All 20 patients completed the study. The average length of diary collection for the 20 randomized patients was 57 days in the Run-in phase and 59 days during the post-randomization phase.

There were no major differences between the placebo and tasimelteon treatment groups in regard to demographic and baseline characteristics of the patients who participated in the Randomized Withdrawal Phase (Table 20). Baseline data was collected during the tasimelteon open-label run-in phase. Summary statements that follow refer to the patients randomized to receive either tasimelteon or placebo unless otherwise specified. Overall, there were 12 males and 8 females.

The mean age was 51.7 years with a range of 27 to 68 years. 90.0% of patients were White. The mean BMI was 28.64 $kg/m^2$.

**Table 20: Demographics and Baseline Characteristics All Patients in RESET**

| | Not Randomized[1] (N=37) | Randomized Withdrawal Phase[2] | | | Total (N=57) |
|---|---|---|---|---|---|
| | | Placebo (N=10) n (%) | Tasimelteon (N=10) n (%) | Total (N=20) n (%) | |
| **Age at screening (years)** | | | | | |
| n | 37 | 10 | 10 | 20 | 57 |
| Mean (SD) | 52.4 (13.18) | 52.1 (12.01) | 51.3 (12.87) | 51.7 (12.12) | 52.1 (12.71) |
| **Age category (n, %)** | | | | | |
| 18 to 40 years | 9 (24.3) | 2 (20.0) | 1 (10.0) | 3 (15.0) | 12 (21.1) |
| 41 to 65 years | 24 (64.9) | 8 (80.0) | 7 (70.0) | 15 (75.0) | 39 (68.4) |
| >65 years | 4 (10.8) | 0 (0.0) | 2 (20.0) | 2 (10.0) | 6 (10.5) |
| **Gender (n, %)** | | | | | |
| Male | 21 (56.8) | 6 (60.0) | 6 (60.0) | 12 (60.0) | 33 (57.9) |
| Female | 16 (43.2) | 4 (40.0) | 4 (40.0) | 8 (40.0) | 24 (42.1) |
| **Race (n, %)** | | | | | |
| American Indian or Alaska Native | 1 (2.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.8) |
| Asian | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Black or African or African American | 5 (13.5) | 1 (10.0) | 0 (0.0) | 1 (5.0) | 6 (10.5) |
| Native Hawaiian or Other Pacific Islander | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| White | 31 (83.8) | 9 (90.0) | 9 (90.0) | 18 (90.0) | 49 (86.0) |
| Other | 0 (0.0) | 0 (0.0) | 1 (10.0) | 1 (5.0) | 1 (1.8) |

| | Not Randomized[1] (N=37) | Randomized Withdrawal Phase[2] | | | Total (N=57) |
|---|---|---|---|---|---|
| | | Placebo (N=10) n (%) | Tasimelteon (N=10) n (%) | Total (N=20) n (%) | |
| **Ethnicity (n, %)** | | | | | |
| Hispanic or Latino | 0 (0.0) | 1 (10.0) | 1 (10.0) | 2 (10.0) | 2 (3.5) |
| Not Hispanic or Latino | 37 (100.0) | 9 (90.0) | 9 (90.0) | 18 (90.0) | 55 (96.5) |
| **Weight at screening (kg)** | | | | | |
| n | 37 | 10 | 10 | 20 | 57 |
| Mean (SD) | 81.16 (14.21) | 80.70 (16.03) | 86.21 (13.36) | 83.46 (14.64) | 81.96 (14.27) |
| **Body mass index at screening (kg/m$^2$)** | | | | | |
| n | 37 | 10 | 10 | 20 | 57 |
| Mean (SD) | 29.35 (4.03) | 28.04 (3.56) | 29.24 (3.25) | 28.64 (3.38) | 29.10 (3.79) |

[1] Demographics and baseline characteristics for the Run-in Phase (All Enrolled Patients).
[2] Demographics and baseline characteristics for the Randomized Withdrawal Phase (ITT Population).
aMT6s = 6-sulfatoxymelatonin; dTSD = daytime total sleep duration; ITT = intent-to-treat; LQ-nTST = lower quartile of subjective nighttime total sleep time; MoST = midpoint of sleep timing; nTST = nighttime total sleep time; UQ-dTSD = upper quartile of subjective daytime total sleep duration; SD = standard deviation.

The mean LQ- nTST, UQ-dTSD, nTST, and dTSD at screening were 5.4 hours, 1.0 hours, 6.8 hours, and 0.3 hours, respectively (Table 21). Patients in the placebo group had a lower mean MoST measurement than patients in the tasimelteon group: 2.9 vs. 3.6. The mean $\tau$ values as measured by urinary aMT6s and cortisol were 24.00 hours each during the run-in phase.

**Table 21: Tasimelteon Run-in Values for RESET Efficacy Parameters**

| | Not Randomized (N=37) | Randomized Withdrawal Phase | | | Total (N=57) |
|---|---|---|---|---|---|
| | | Placebo (N=10) n (%) | Tasimelteon (N=10) n (%) | Total (N=20) n (%) | |
| **Average of LQ-nTST during run-in phase (hours)** | | | | | |
| n | 31 | 10 | 10 | 20 | 51 |
| Mean (SD) | 4.26 (1.38) | 5.34 (1.36) | 5.51 (0.94) | 5.43 (1.14) | 4.72 (1.40) |
| Median | 4.28 | 5.27 | 5.36 | 5.33 | 5.00 |
| **Average of UQ-dTSD during run-in phase (hours)** | | | | | |
| n | 30 | 10 | 10 | 20 | 50 |
| Mean (SD) | 1.50 (1.28) | 0.99 (0.90) | 0.96 (1.11) | 0.98 (0.98) | 1.29 (1.19) |
| Median | 1.15 | 0.89 | 0.87 | 0.89 | 0.99 |
| **Average of nTST during run-in phase (hours)** | | | | | |
| n | 31 | 10 | 10 | 20 | 51 |
| Mean (SD) | 5.90 (0.92) | 6.80 (1.03) | 6.81 (0.86) | 6.81 (0.92) | 6.26 (1.02) |
| Median | 6.06 | 6.95 | 6.92 | 6.93 | 6.29 |
| **Average of dTSD during run-in phase (hours)** | | | | | |
| n | 30 | 10 | 10 | 20 | 50 |
| Mean (SD) | 0.61 (0.60) | 0.35 (0.28) | 0.34 (0.45) | 0.35 (0.36) | 0.50 (0.53) |
| Median | 0.36 | 0.31 | 0.27 | 0.29 | 0.32 |
| **MoST during run-in phase (hours)** | | | | | |
| n | 31 | 10 | 10 | 20 | 51 |
| Mean (SD) | 3.16 (0.90) | 2.91 (1.01) | 3.63 (0.96) | 3.27 (1.03) | 3.20 (0.94) |
| Median | 3.19 | 3.08 | 3.79 | 3.60 | 3.21 |
| **τ (aMT6s)** | | | | | |
| n | 28 | 10 | 10 | 20 | 48 |
| Mean (SD) | 24.52 (0.33) | 23.99 (0.03) | 24.00 (0.04) | 24.00 (0.04) | 24.30 (0.36) |
| Median | 24.49 | 23.99 | 24.00 | 23.99 | 24.19 |
| **τ (cortisol)** | | | | | |
| n | 20 | 10 | 10 | 20 | 40 |
| Mean (SD) | 24.48 (0.27) | 23.99 (0.08) | 24.01 (0.09) | 24.00 (0.08) | 24.24 (0.31) |
| Median | 24.44 | 24.00 | 24.01 | 24.00 | 24.12 |

### 6.2.4. Statistical Methods

A Statistical Analysis Plan was finalized prior to database lock and completion of the final analyses.

Summary statistics include the mean, N, standard deviation, median, minimum, and maximum values for continuous variables, and frequencies and percentages for categorical variables. Statistical analyses were performed using two-sided tests. A 0.05 significance level was used in all tests of treatment differences.

Confidence intervals are two-sided with 95% confidence. No adjustment for multiplicity was done. P-values will be reported for reference purposes, and are presented to four (4) decimal places and reported as <.0001 if it is less than 0.0001.

The following analysis populations were defined for analysis purposes:

**Intent-to-Treat (ITT) Population**: The Intent-to-Treat Population will include all subjects randomized into the study that have $\tau$ estimated post-randomization.

**Safety Population for the Tasimelteon Run-in Phase:** The Safety Population for the tasimelteon Run-in Phase included all patients who entered the tasimelteon Run-in Phase and received at least one dose of study drug.

**Safety Population for the Randomized Withdrawal Phase:** The Safety Population for the Randomized Withdrawal Phase included all patients who entered the Randomized Withdrawal Phase and received at least one dose of randomized study drug.

**Analysis of Efficacy Measures**

The primary efficacy endpoint is defined as the proportion of subjects who became non-entrained to a 24-hour day after randomization to tasimelteon or placebo. Hence, the primary null hypothesis is that no difference exists in the proportion of people with "non-entrained" circadian rhythms between subjects receiving tasimelteon and subjects receiving placebo.

The cortisol non-entrainment secondary endpoint was summarized and analyzed in the same manner of the primary endpoint in the ITT population.

For the continuous efficacy variables, descriptive statistics were presented by treatment groups. Treatment groups were compared using an analysis of covariance (ANCOVA)

model with the terms of treatment group and the corresponding efficacy value in Run-in phase as a covariate. These analyses were conducted in the ITT Population.

The secondary endpoint of circadian cycle time to first relapse event was analyzed via Kaplan-Meier product-limit survival curve estimates and an unstratified log-rank test for treatment group comparison. Circadian cycle time is based on an individual's $\tau$, e.g., a person with $\tau$= 25 has a 24 day circadian cycle compared to a person with a $\tau$ = 24.5 who has a 48 day circadian cycle. Fifty percent of one circadian cycle would then be 12 days and 24 days respectively for the example above.

Subjects who did not meet the criteria for a relapse event (relapse event being defined as a 45 minute decrement in their weekly average of nTST) during the Randomized Withdrawal phase were censored at the cycle time of the discontinuation or completion of the study. The null hypothesis states there is no difference between the treatment groups on the distribution of cycle time to relapse. In addition, a Kaplan-Meier curve for cycle time to relapse was plotted. A similar analysis, including the Kaplan-Meier plot, was also done with actual calendar time to first relapse.

### 6.2.5. Efficacy Results, RESET

Non-24 patients that entrain to tasimelteon treatment quickly become non-entrained as measured beginning at week three post-randomization when placed on placebo, while those patients that remain on tasimelteon treatment maintain entrainment. In the RESET randomized withdrawal study, the primary endpoint, defined as maintenance of effect of tasimelteon to entrain circadian rhythms in patients with Non-24 as measured by urinary aMT6s, was achieved. 90% of tasimelteon treated patients remained entrained compared to 20% of placebo treated patients. This proportion was statistically significantly different between the treatments (difference = -70.0%; p = 0.0026).

**Table 22: Summary of Primary Efficacy Endpoint, RESET Study**

| Statistic | Placebo n/N′ (%) | Tasimelteon 20 mg n/N′ (%) | P-value[1] | P-value[2] |
|---|---|---|---|---|
| Maintenance of entrainment rate[3] | 2/10 (20.0) | 9/10 (90.0) | 0.0026 | 0.0055 |

[1] P-value was based on Barnard's Exact Test, two-sided.
[2] P-value was based on Fisher's exact test, two-sided
[3] Not entrained is defined as having a post-baseline $\tau$ value $\geq$ 24.1 or the lower bound of the 95% CI > 24.0 hours.

### 6.2.6. Key Secondary Results, RESET

#### 6.2.6.1. Tasimelteon Maintains Entrainment of Cortisol Circadian Rhythms

The circadian period of cortisol was measured during screening and post-randomization. Similar to aMT6s, all patients who were randomized in RESET for whom there was a measured cortisol τ value (19/20) had entrained cortisol rhythms during the tasimelteon run-in phase (τ value < 24.1 hours and the lower bound of the 95% CI includes 24.0 hours). Non-entrainment was defined as having a post-baseline τ value ≥ 24.1 hours or the lower bound of the 95% CI >24.0 hours. Only 2/10 (20%) of tasimelteon treated patients became un-entrained versus 8/10 (80%) of placebo treated patients. This proportion was statistically significantly different between the treatments (% difference = -60.0; p = 0.0118), Table 23. This demonstrates that chronic dosing of tasimelteon is required to maintain entrainment of circadian rhythms such as that of cortisol.

**Table 23: Maintenance of Entrainment as Measured by Cortisol**

| Category Statistic | Placebo (N=10) | Tasimelteon 20 mg (N=10) | Treatment Difference (Tasimelteon minus Placebo) | P-value[1] |
|---|---|---|---|---|
| Maintenance of entrainment rate (cortisol) n (%)[2] | 2/10 (20.0) | 8/10 (80.0) | -60.0 | 0.0118 |

[1] P-value was based on Barnard's Exact Test, two-sided.

[2] Not entrained is defined as having a post-baseline τ value ≥ 24.1 or the lower bound of the 95% CI > 24.0 hours.

### 6.2.6.2. Sleep-Wake Secondary Endpoints, RESET

**Table 24: Summary of Sleep-Wake Secondary Efficacy endpoints (ITT Population), RESET Study**

| Statistic | Placebo (N=10) | Tasimelteon 20 mg (N=10) | Treatment Difference (Tasimelteon minus Placebo) | P-value |
|---|---|---|---|---|
| LQ-nTST (LS mean minutes)[1] | -73.74 | -6.74 | 67.00 | 0.0233 |
| UQ-dTSD (LS mean minutes) [1] | 49.95 | -9.31 | -59.25 | 0.0266 |
| MoST (LS mean minutes) [1] | -16.05 | 19.99 | 36.04 | 0.0108 |
| nTST (LS mean minutes) [1] | -44.49 | -12.23 | 32.26 | 0.1315 |
| dTSD (LS mean minutes) [1] | 17.85 | -3.12 | -20.97 | 0.0547 |
| Non-entrained[2] and ≥30 minute decrement in nTST n (%)[3] | 5/10 (50.0) | 1/10 (10.0) | -40.0 | 0.0623 |

[1] P-value was based on analysis of covariance model.
[2] Non-entrained is defined as having a post-baseline τ value of ≥ 24.1 or the lower bound of the 95% CI > 24.0 hours.
[3] P-value was based on Barnard's exact test, two sided.
dTSD = daytime total sleep duration; LQ-nTST = lower quartile of subjective nighttime total sleep time; LS mean = least-squares mean; MoST = midpoint of sleep timing; nTST = nighttime total sleep time; UQ-dTSD = upper quartile of subjective daytime total sleep duration.

**Tasimelteon Maintains Improvements in Nighttime Total Sleep Time (nTST)**

Worsening was defined as non-entrainment and a ≥30 minute decrement in nTST. The proportion of patients who worsened after tasimelteon treatment during the Randomized Withdrawal Phase was numerically less than the proportion of patients who worsened after placebo treatment (% difference = -40.0; p = 0.0623, Barnard's Exact Test).

The Least Square (LS) mean change from baseline (Run-in Phase) in nTST during the Randomized Withdrawal Phase was statistically significant after placebo treatment (LS mean change = -0.74 hours [-44.49 minutes]; p = 0.0066) but not after tasimelteon treatment (LS mean change = -0.20 hours [-12.23 minutes]; p = 0.4074). The decrease in LS mean from baseline in nTST after tasimelteon treatment during the Randomized Withdrawal Phase was numerically less than the LS mean change from baseline in nTST after placebo treatment (LS mean difference = 0.54 hours [32.26 minutes]; p = 0.1315 [ANCOVA]).

**Tasimelteon Maintains Improvements in the Worst 25% of Nighttime Total Sleep Time (LQ-nTST)**

The LS mean change from baseline (Run-in Phase) in LQ-nTST during the Randomized Withdrawal Phase was statistically significant after placebo treatment (LS mean change = -1.23 hours [-73.74 minutes]; p = 0.0012) but not after tasimelteon treatment (LS mean change = -0.11 hours [-6.74 minutes]; p = 0.7269). The LS mean change from baseline in LQ-nTST after tasimelteon treatment during the Randomized Withdrawal Phase was statistically significantly less than the LS mean change from baseline in LQ-nTST after placebo treatment (LS mean difference = 1.12 hours [67.00 minutes]; p = 0.0233 [ANCOVA]).

**Tasimelteon Maintains Improvements in Daytime Total Sleep Duration (dTSD)**

Patients who randomized to placebo during the Randomized Withdrawal Phase experienced an increase in daytime sleep duration compared to the Run-in Phase while patients who were randomized to tasimelteon experienced a further reduction in excessive daytime sleep duration compared to the Run-in Phase with continued tasimelteon treatment.

The LS mean change from baseline (Run-in Phase) in dTSD during the Randomized Withdrawal Phase was statistically significant after placebo treatment (LS mean change = 0.30 hours [17.85 minutes]; p = 0.0237) but not after tasimelteon treatment (LS mean change = -0.05 hours [-3.12 minutes]; p = 0.6700). The LS mean change from baseline in dTSD after tasimelteon treatment during the Randomized Withdrawal Phase was numerically less than the LS mean change from baseline in dTSD after placebo treatment (LS mean difference = -0.35 hours [-20.97 minutes]; p = 0.0547 [ANCOVA]).

**Tasimelteon Maintains Improvements in Worst 25% of Daytime Total Sleep Duration (UQ-dTSD)**

The LS mean change from baseline (Run-in Phase) in UQ-dTSD during the Randomized Withdrawal Phase was statistically significant after placebo treatment (LS mean change = 0.83 hours [49.95 minutes]; p = 0.0101) but not after tasimelteon treatment (LS mean change = -0.16 hours [-9.31 minutes]; p = 0.5966). The LS mean change from baseline in UQ-dTSD after tasimelteon treatment during the Randomized Withdrawal Phase was statistically significantly less than the LS mean change from baseline in UQ-dTSD after placebo treatment (LS mean difference = -0.99 hours [-59.25 minutes]; p = 0.0266 [ANCOVA]).

**Tasimelteon Maintains Improvements in the Timing of Sleep (MoST)**

Treatment with placebo resulted in a decrease in midpoint of sleep timing while treatment with tasimelteon resulted in a further increase in midpoint of sleep timing. The LS mean increase from baseline (Run-in Phase) in MoST during the Randomized Withdrawal Phase was statistically significant after tasimelteon treatment (LS mean change = 0.33 hours [19.99 minutes]; p = 0.0330) but not after placebo treatment (LS mean change = -0.27 hours [-16.05 minutes]; p = 0.0797). The LS mean change from baseline in MoST after tasimelteon treatment during the Randomized Withdrawal Phase was statistically significantly greater than the LS mean change from baseline in MoST after placebo treatment (LS mean difference = 0.60 hours [36.04 minutes]; p = 0.0108 [ANCOVA]).

### 6.2.6.3. Time to first relapse event, RESET

A patient was defined as relapsed if the patient experienced a 45 minute or greater decrement in weekly average subjective nTST compared to the Run-in Phase. The last day of the week during which relapse occurred was considered the actual time of relapse. Patients who did not experience relapse were censored on the last day of the last week that nTST was calculated. Circadian time was calculated as 100*(actual time/circadian cycle length) where circadian cycle length was determined based on the τ estimated during the screening period for SET.

Circadian cycle length in days was calculated as follows:

$$\text{Circadian cycle length} = 24 \text{ hours} \div (\tau - 24.0 \text{ hours}) / 1 \text{ day}$$

For an individual with a τ of 24.0 hours, their circadian phase at midnight on day 1 would be identical to their circadian phase at midnight on day 2. Thus their circadian cycle length would be 1 day. A person with a τ of 25.0 hours delays one hour each day and thus it would take 24 days for their circadian phase to align with midnight in the same manner as on day 1 (24.0/25.0-24 = 24). Similarly, a person with a τ of 24.5 hours would have a circadian cycle length of 48 days (Table 1).

**Table 25: Time to Relapse Survival Analysis**

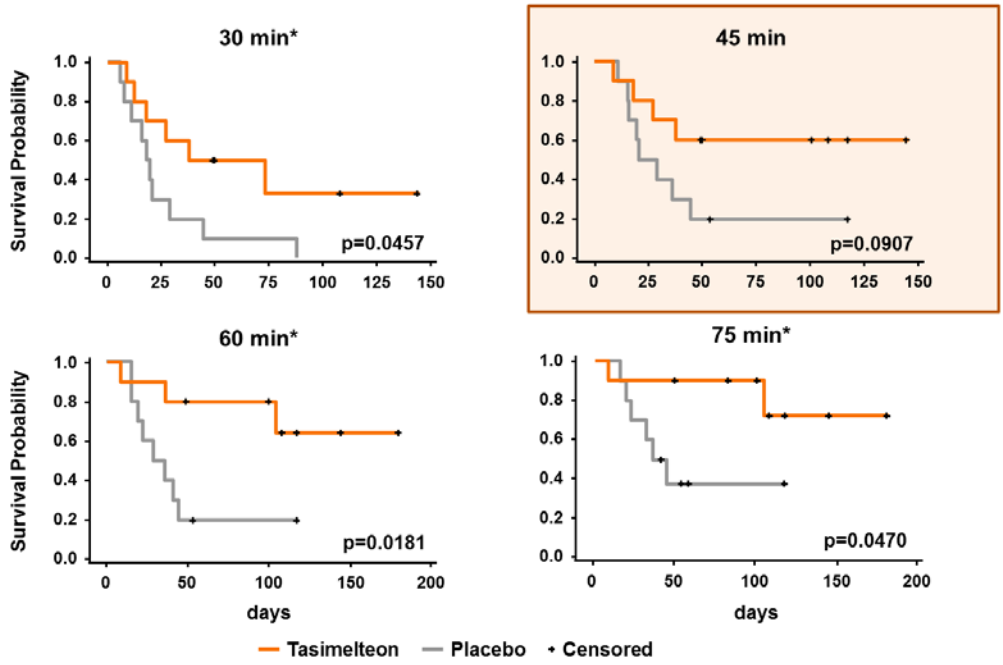
| Statistic | Placebo (N=10) | Tasimelteon 20 mg (N=10) | Treatment Difference (Tasimelteon minus Placebo) | P-value[1] |
|---|---|---|---|---|
| Circadian time to first relapse[2] (median percentage of cycle) | 24.7 | NE | NA | 0.0907 |
| Actual time to first relapse[2] (median weeks) | 4.0 | NE | NA | 0.1481 |
| Circadian time to first relapse (alternate definition)[3](median percentage of cycle) | 32.4 | NE | NA | 0.0181 |

[1] P-value was based on log-rank test
[2] Time to relapse with relapse defined as a 45 minute or greater decrement in the weekly average of nTST compared to the Run-in Phase.
[3] Time to relapse with relapse defined as a 60 minute or greater decrement in the weekly average of nTST compared to the Run-in Phase.

The tasimelteon treatment group was numerically superior to the placebo group in the delay of patient's relapse which is defined as a 45 minute or greater decrement in weekly average subjective nTST compared to the Run-in Phase. A sensitivity analysis, the treatment difference for actual time to relapse did not separate from placebo (p = 0.1481) when measured as a 45 minute or greater decrement in weekly average subjective nTST compared to the Run-in Phase (Table 25). Additionally in a sensitivity analysis, the treatment difference for circadian time to relapse was statistically significant (p = 0.0181) when measured as a 60 minute or greater decrement in weekly average subjective nTST compared to the Run-in Phase (Table 25).

Figure 22 presents the Kaplan-Meier curve of circadian time (%) to the first relapse event for the ITT Population for a 45 minute decrement (highlighted box). Sensitivity analyses are also presented in Figure 22 with 30 min, 60 min and 75 min decrements in the nTST as the threshold for time to relapse. A higher percentage of patients in the placebo group had a relapse event and at an earlier time point (as measured by circadian and actual time) compared to patients in the tasimelteon group for the pre-specified endpoint and all of the sensitivity analyses. The data in Figure 22 is predicted consistent with the loss of entrainment of the Master clock in patients who are withdrawn from tasimelteon treatment. All of the placebo patients who relapsed did so by the time they were 50% through their circadian cycle (e.g. when their body clock was most out of synchrony with the 24-hour day).

**Figure 22: Kaplan-Meier Curves of Circadian Time (100%) to First Relapse Event, RESET Study**




*Exploratory analyses

A subject is defined as relapsed if the subject experienced a 30, 45 (pre-specified secondary endpoint), 60, or 90 minute or greater decrement in weekly average subjective nighttime total sleep time (nTST) compared to the Run-in Phase. The last day of the week during which relapse occurred is considered the actual time of relapse. Subjects who do not experience relapse are censored on the last day of the last week that nTST was calculated. Circadian time is calculated as 100% (actual time/circadian cycle length) when circadian cycle length is determined based on the τ estimated during the screening period for the SET study.

**Two Patients Treated with Tasimelteon Followed for over 500 Days**

- Patient 1: Screening-randomized tasimelteon-open-label tasimelteon-placebo
- Patient 2: Screening: open-label tasimelteon- open-label tasimelteon-placebo

Two patients are presented in Figure 23 and Table 26 with entrained circadian rhythms and improved clinical measures of LQ-nTST and UQ-dTSD with tasimelteon treatment. Tasimelteon withdrawal during the RESET Study results in a loss of entrainment and clinical benefit.

The format for the raster plots are similar to those previously described. Patients were required to collect sleep data for 2.5 circadian cycles or 6 months, whichever was less. Patients resumed reporting sleep diary data during week 6 of the RESET Run-in phase. The period patients were not required to collect sleep-wake data is represented by the gap between green nighttime sleep recordings.

Patient 3 had a baseline $\tau$ =24.55 (95% CI: 24.42 to 24.69) and a cyclical sleep-wake pattern that was most disturbed when the patient was out-of-phase, i.e. aMT6s acrophase values occurring during daytime hours. During the Double-Masked Phase of SET the patient's nighttime sleep pattern stabilized and the compulsory daytime sleep episodes dissipated. LQ-nTST had a maximal improvement of 3.32 hours from baseline and UQ-dTSD decreased by as much as 4.28 hours during the RESET Run-in (Table 26). The patient had a N24CRS score of four in SET and entrained circadian rhythms when assessed at month seven, 23.99 (95% CI: 23.94 – 24.04), but not at Month 1. The daytime sleep pattern and an extrapolation of a line drawn through the red stars suggest that the patient was not in-phase when tasimelteon treatment was initiated. Her aMT6s acrophase values were predicted to be at approximately 18:00 hours when treatment was initiated. Treatment initiation out of phase may explain why they were not entrained when assessed during month 1 of treatment, but took slightly longer to respond.

Immediately upon withdrawal of tasimelteon, in the RESET Double-Masked Phase, this patient experienced sleep latency problems, excessive compulsory daytime sleep episodes and a daily delaying of their aMT6s acrophase (red stars). Her LQ-nTST decreased to near baseline levels of 2.75 hours/night and their UQ-dTSD increased to 4.43 hours/day.

Patient 4 was a subject enrolled in the SET open label arm. A baseline $\tau$ value of 24.19 (95% CI: 24.15- 24.24) made them ineligible for the Double-Masked Phase. The raster plot demonstrates a significant dissipation of daytime sleep and an increase in nighttime sleep, mostly as a result of a decrease in early morning awakenings, with tasimelteon treatment. LQ-nTST increases by 2.15 hours and UQ-dTSD decreases by 0.58 hours between SET baseline and the RESET Run-in phase (Table 26). Her circadian rhythms were entrained when assessed during the RESET Run-in phase, $\tau$ = 24.02 (95% CI: 23.99- 24.05). Entrainment status was not assessed in SET because they were in the Open Label Arm. Tasimelteon withdrawal resulted in immediate non-entrainment of her circadian rhythms [24.19 (95% CI: 24.02-24.36)] and a relapse of her sleep-wake problems (Table 26).

Both patients demonstrate efficacy of tasimelteon to entrain circadian rhythms, provide clinically meaningful benefit in sleep-wake measures, and the need for daily dosing to maintain the treatment effect in Non-24 patients with total blindness.

**Figure 23: Raster Plots of Two Patients that Respond to Tasimelteon Treatment then Relapse on Placebo**

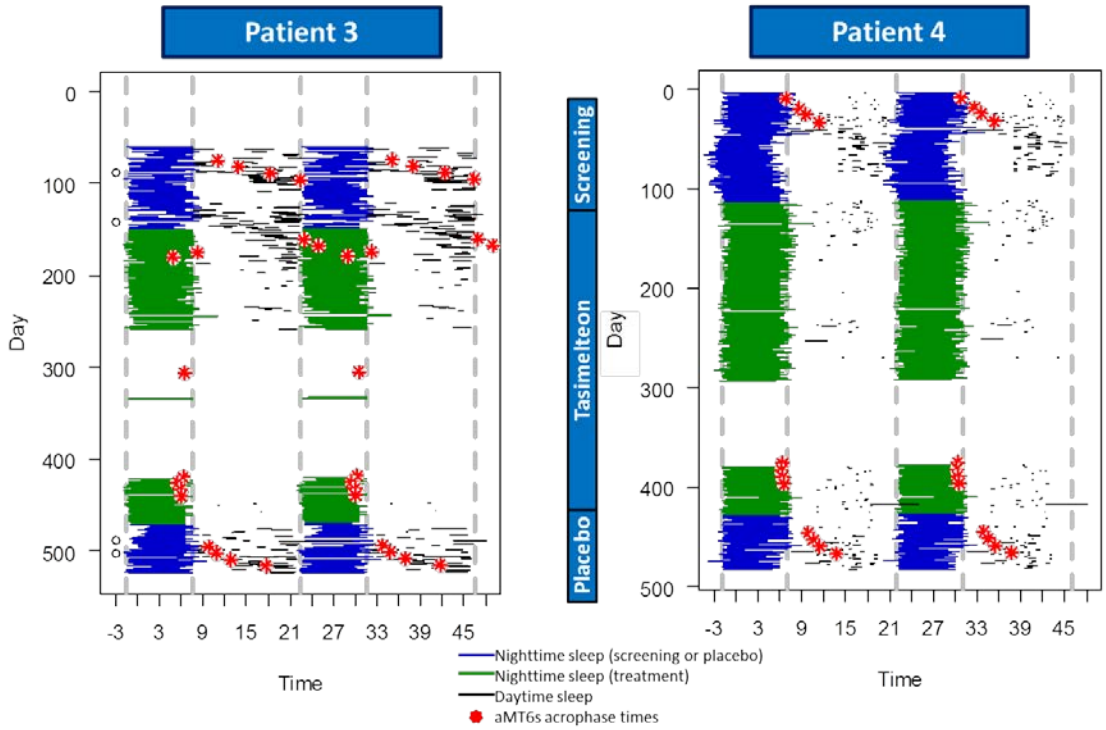


**Table 26: Average LQ-nTST and UQ-dTSD for Patients 3 and 4 in Figure 23**

| | Patient 3 | | Patient 4 | |
|---|---|---|---|---|
| **STUDY Phase** | **LQ-nTST (hours)** | **UQ-dTSD (hours)** | **LQ-nTST (hours)** | **UQ-dTSD (hours)** |
| SET Screening | 2.85 | 4.32 | 5.27 | 1.43 |
| SET Tasimelteon | 5.02 | 2.54 | 7.06 | 0.37 |
| RESET Tasimelteon Run-in | 6.17 | 0.04 | 7.42 | 0.85 |
| RESET Placebo | 2.75 | 4.43 | 4.11 | 1.57 |

### 6.2.7. Efficacy Conclusions, RESET

Overall, the results of this study provide robust evidence of the maintenance of effect of continued treatment with tasimelteon 20 mg in patients with Non-24. Tasimelteon treatment is necessary for both induction and maintenance of entrainment and for maintenance of clinical benefits in sleep and wake measures.

- Tasimelteon-treated patients maintained entrainment status at significantly higher rates than placebo-treated patients;
- Tasimelteon was significantly associated with the delay of relapse in total sleep time as compared to placebo;
- Tasimelteon was associated with a lower rate of non-entrainment of the cortisol rhythm as compared to placebo during the randomized withdrawal;
- Tasimelteon demonstrated continued clinical improvements across a number of sleep and wake parameters including measures of daytime total sleep duration, the upper quartile of daytime sleep duration, and timing of sleep between the Run-in Phase and Randomized Withdrawal Phase;
- Withdrawal of tasimelteon treatment resulted in a significant decrease in sleep in the worst quartile of nights (LQ-nTST), a significant increase in excessive daytime sleep duration in the worst quartile of days (UQ-dTSD), and a significantly negative impact on the timing of sleep relative to desired bedtimes (MoST).

## 6.3. Recommended length to treatment trial

Time to response may be influenced by an individual's endogenous circadian cycle length as well as the point in their cycle during which dosing is initiated (13, 24-28). A circadian cycle length is defined as the number of days between two consecutive alignments of the Master clock to the 24-hour day (Table 1). In healthy individuals, the circadian cycle length is equal to one day.

Entrainment of the Master clock may be immediate, or it may require treatment with tasimelteon for one full circadian cycle. The individual nature of circadian rhythms, including cycle length and phase timing, make an adequate trial important in optimizing the extent and the timing of patient outcomes. While cycle lengths generally ranged from 27–184 days in the clinical trials, the majority of patients studied had a cycle length between 40-80 days (based on 1 standard deviation from the mean). Therefore, an adequate length to trial treatment is at least 80 days. It is expected that entrainment of the Master clock by tasimelteon will be faster if patients initiate treatment when their sleep and wake patterns begin to normalize or otherwise they are in-phase.

## 6.4. Other Requested Analyses

### 6.4.1. ITT* Analyses

For the pre-NDA meeting the FDA requested that a sensitivity analysis using the ITT* population for Study 3201 be conducted. The ITT* analysis is consistent with the Per-Protocol analyses and is statistically significant for the primary endpoints and the key secondary endpoints. These results support the efficacy of tasimelteon in the treatment of Non-24. (Table 27 Table 28, and Table 29).

**Table 27: Protocol, ITT and ITT* Analyses for Primary Endpoints and Associated Sensitivity Analyses**

| Category Statistic | Entrainment[1] (aMT6s) | Clinical Response (Entrainment[2] +N24CRS >= 3) | Clinical Response (Entrainment[2] + N24CRS ≥ 2) | N24CRS ≥ 3 | N24CRS ≥ 2 |
|---|---|---|---|---|---|
| **Per-protocol**[3] | | | | | |
| **p-value** | 0.0171 | 0.0028 | 0.0006 | 0.0031 | 0.0014 |
| **Tasimelteon (%)** | 8/40 (20.0) | 9/40 (23.7) | 11/40 (28.9) | 11/40 (28.9) | 22/40 (57.9) |
| **Placebo (%)** | 1/38 (2.6) | 0/38 (0.0) | 0/38 (0.0) | 1/38 (2.9) | 7/38 (20.6) |
| **ITT** | | | | | |
| **p-value** | 0.0171 | 0.002 | 0.0004 | 0.0023 | 0.0009 |
| **Tasimelteon (%)** | 8/40 (20.0) | 9/40 (22.5) | 11/40 (27.5) | 11/40 (27.5) | 22/40 (55.0) |
| **Placebo (%)** | 1/38 (2.6) | 0/38 (0) | 0/38 (0) | 1/38 (2.6) | 7/38 (18.4) |
| **ITT*** | | | | | |
| **p-value** | 0.0171 | 0.002 | 0.0004 | 0.0065 | 0.0034 |
| **Tasimelteon (%)** | 8/40 (20.0) | 9/40 (22.5) | 11/40 (27.5) | 11/42 (26.2) | 22/42 (52.4) |
| **Placebo (%)** | 1/38 (2.6) | 0/38 (0) | 0/38 (0) | 2/42 (4.8) | 9/42 (21.4) |

[1] Entrainment status from the randomized portion of SET.
[2] Entrainment status from Month 1 and Month 7
[3] Population that was pre-specified in the SET Study (ITT for entrainment analyses and Analysis Population for N24CRS).
ITT= Intent t-to-treat population as defined in SET (all randomized patients who have τ calculated post-randomization); ITT *= Intent-to-treat population (all patients who received at least one dose of treatment and had one assessment); aMT6s = 6-sulfatoxymelatonin; SAP = Statistical analysis plan; N24CRS = Non-
24 Clinical Response Scale.

**Table 28: Per Protocol, ITT, and ITT* Analyses for Cortisol, CGI-C. and MoST Endpoints**

| Category Statistic | Entrainment (cortisol) (%) | CGI-C[1] (LS mean) | MoST (LS mean minutes) |
|---|---|---|---|
| **Per-protocol**[2] | | | |
| **p-value** | 0.0313 | 0.0093 | 0.0123 |
| **Tasimelteon (%)** | 7/40 (17.5) | 2.6 | 35.00 |
| **Placebo (%)** | 1/38 (2.6) | 3.4 | 14.48 |
| **ITT** | | | |
| **p-value** | 0.0313 | 0.0086 | 0.0470 |
| **Tasimelteon (%)** | 7/40 (17.5) | 2.6 | 33.83 |
| **Placebo (%)** | 1/38 (2.6) | 3.4 | 16.49 |
| **ITT*** | | | |
| **p-value** | 0.0313 | 0.0104 | 0.0229 |
| **Tasimelteon (%)** | 7/40 (17.5) | 2.6 | 33.79 |
| **Placebo (%)** | 1/38 (2.6) | 3.4 | 13.01 |

[1] For CGI-C smaller numbers indicate improvement.
[2] Population that was pre-specified in the SET Study (ITT for entrainment analyses and Analysis Population for all clinical endpoints).
ITT= Intent t-to-treat population as defined in SET (all randomized patients who have τ calculated post-randomization); ITT* = Intent-to-treat population (all patients who received at least one dose of treatment and had one assessment); SAP = Statistical analysis plan; LS = Least square; CGI-C = Clinical global impression of change; MoST = Midpoint of sleep timing.

**Table 29: Per Protocol, ITT, and ITT* Analyses For Nighttime and Daytime Sleep Measures**

| Category Statistic | LQ-nTST and UQ- dTSD ≥ 90 min[1] (%) | LQ-nTST and UQ- dTSD ≥ 45 min (%) | LQ-nTST (LS mean minutes) | UQ-dTSD[2] (LS mean minutes) |
|---|---|---|---|---|
| **Per-protocol**[3] | | | | |
| **p-value** | 0.0767 | 0.0177 | 0.0055 | 0.0050 |
| **Tasimelteon (%)** | 5/40 (13.2) | 12/40 (31.6) | 56.80 | -46.48 |
| **Placebo (%)** | 1/38 (2.9) | 3/38 (8.8) | 17.08 | -17.87 |
| **ITT** | | | | |
| **p-value** | 0.0577 | 0.0169 | 0.0034 | 0.0029 |
| **Tasimelteon (%)** | 5/22 (22.7) | 12/40 (30.0) | 56.50 | -46.83 |
| **Placebo (%)** | 1/25 (4.0) | 3/38 (7.9) | 14.83 | -15.79 |
| **ITT*** | | | | |
| **p-value** | 0.1733 | 0.063 | 0.0232 | 0.0031 |
| **Tasimelteon (%)** | 5/24 (20.8) | 12/42 (28.6) | 53.16 | -50.45 |
| **Placebo (%)** | 2/28 (7.14) | 5/42 (11.9) | 17.35 | -16.94 |

[1] For this endpoint, only patients with significant nighttime sleep and daytime sleep problems at baseline were included, this was a post-hoc analysis.
[2] For UQ-dTSD smaller numbers indicate improvement.
[3] Population that was pre-specified in the SET Study (ITT for entrainment analyses and Analysis Population for all clinical endpoints).
ITT= Intent t-to-treat population as defined in SET (all randomized patients who have τ calculated post-randomization); ITT* = Intent-to-treat population (all patients who received at least one dose of treatment and had one assessment); SAP = Statistical analysis plan; LS = Least square; LQ-nTST = Lower quartile of nighttime total sleep time; UQ-dTSD = Upper quartile of daytime total sleep duration;

### 6.4.2. Analyses of In-Phase and Out-of-Phase

During the NDA review the FDA noted

> *"In Study 3201*[SET]*, the lengths of circadian cycle varied among the enrolled subjects. Circadian cycle length expressed as a percentage (actual time/circadian cycle length) is a potential means of comparing effects at a given point in a circadian cycle in one subject to a similar time point in another subject. For example, the time point at 50% circadian cycle time is when patients are expected to be most symptomatic since the endogenous circadian rhythm is most out-of sync with the 24-hour day, and time points 0% or 100% are when there is synchronization."*

The FDA requested that the following post-hoc analysis be conducted:

> *"For each randomized subject who was in the trial for at least 70% of the duration of his/her first circadian cycle in the randomization period in Study 3201, use all available nTST data collected between the time points at 0% and 20% of the first circadian cycle to calculate the mean, and all available nTST data collected between the time points 50% to 70% of first circadian cycle to calculate the mean. The difference between these two means is a reflection of the most symptomatic phase after correcting for the within subject most-likely-to-be asymptomatic period. Do similar analysis for subjects with a second circadian cycle in the randomized phase. Provide a summary of these means (0%-20%, 50%-70%, difference between these means) for the first cycle, and then for the second cycle if available, for each subject by treatment group."*

**Vanda Response to FDA Request for Analyses of In-Phase and Out-of-Phase**

Non-24 patients experience periodic disruptions of their sleep-wake cycle as a result of their inability to entrain their circadian rhythms to a 24-hour day. These periodic disruptions can be described by in-phase or out-of-phase segments. In the requested analysis, in-phase is defined as a segment from 0-20 % of the cycle with 0 being the time in the cycle where the aMT6s acrophase is in perfect alignment with the external clock. Similarly, out-of-phase is defined as the segment from 50-70% of the circadian cycle.

The requested analysis is reasonable however a few considerations related to predicting phase make this analysis challenging. The reasons and impact of the inability to precisely predict timing of acrophase at future time points will be explained in the following paragraphs along with an alternative analysis that can reasonably address the question.

In order to perform the requested analysis, one would need to know when the 0 point of alignment (in-phase) occurs for every patient randomized in the study. While an effort

was made to randomize patients close to the 0 point of alignment, that was not always possible to accurately predict.

Predictions of future timing of acrophase were made based on the timing of the observed acrophase during the measurement of τ. Measurement of τ was performed during the screening period over approximately 4 successive weeks. Measurement of τ is expressed as a mean value derived from a linear regression, accompanied by a 95% confidence interval (CI) around the position of that mean value. This measurement was precise enough to determine whether a patient was not-entrained ($\tau > 24.0$) but was not precise enough to predict where the acrophase will be several weeks later. While on the face of it predicting phase in the future may appear to have a relatively small error, when it is projected over time, as shown in Figure 24 the error of estimating the future position of the acrophase is very large. This suggests that using the available τ measurements to predict whether a patient is in-phase or out-of-phase at the time of randomization may result in some imprecise estimates of timing of "in-phase" for some patients.

In Figure 24 τ is estimated based on data collected up until Day 29. This data predicts an acrophase position estimate at Day 66 to be in-phase (blue line represents Day 66; gray horizontal line represents the acrophase time when patient is in-phase). However, as demonstrated by the widening of the confidence interval over this time course between Day 29 and Day 66, at day 66 the 95% confidence interval spans almost 24 hours. This means that at the time of randomization this patient's acrophase could be occurring at almost any time during the day, e.g. they could be either in-phase or out-of-phase. Furthermore, Figure 25, a composite of the patient's raster plot (c) and nTST (a) and dTSD (b) scatter plots demonstrate that this patient was randomized when they were out-of-phase. A single dot is plotted for each night or day in the scatter plots. As a result the requested analysis using the Diff (in-out) amount of sleep will result in a highly negative value and categorize this individual as a (*negative)* super responder. Further inspection of the raster plot demonstrates that this conclusion is incorrect as this patient's sleep pattern continues to have the same cyclical and pathological profile during the Double-masked phase as they did during screening, consistent with no treatment effect.

**Figure 24: Confidence Interval of Phase Predictions over Time**

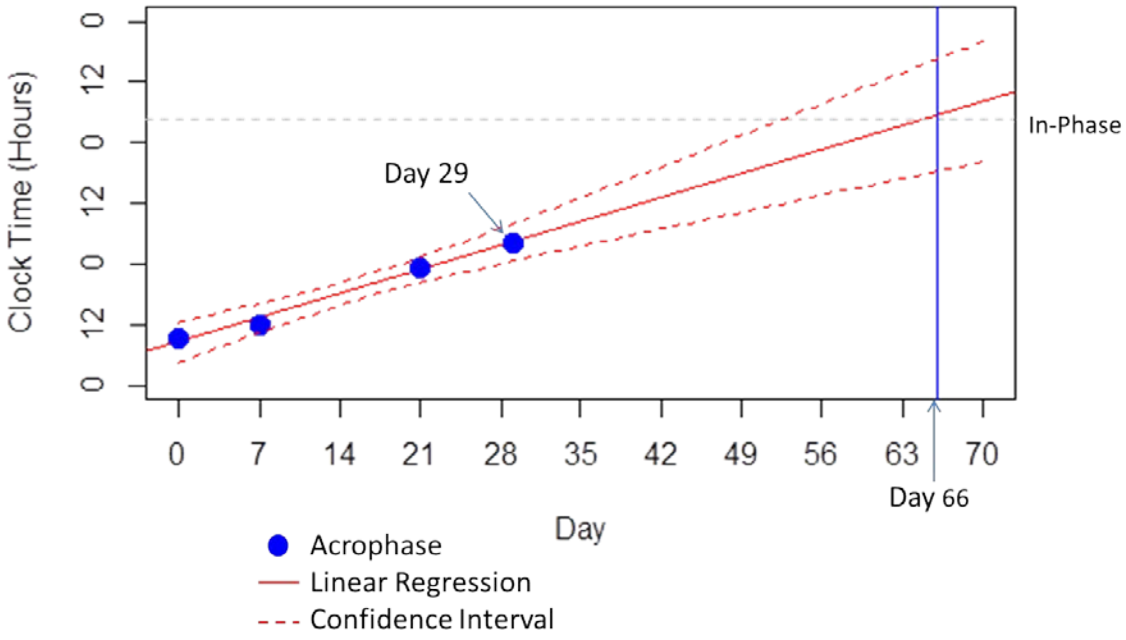
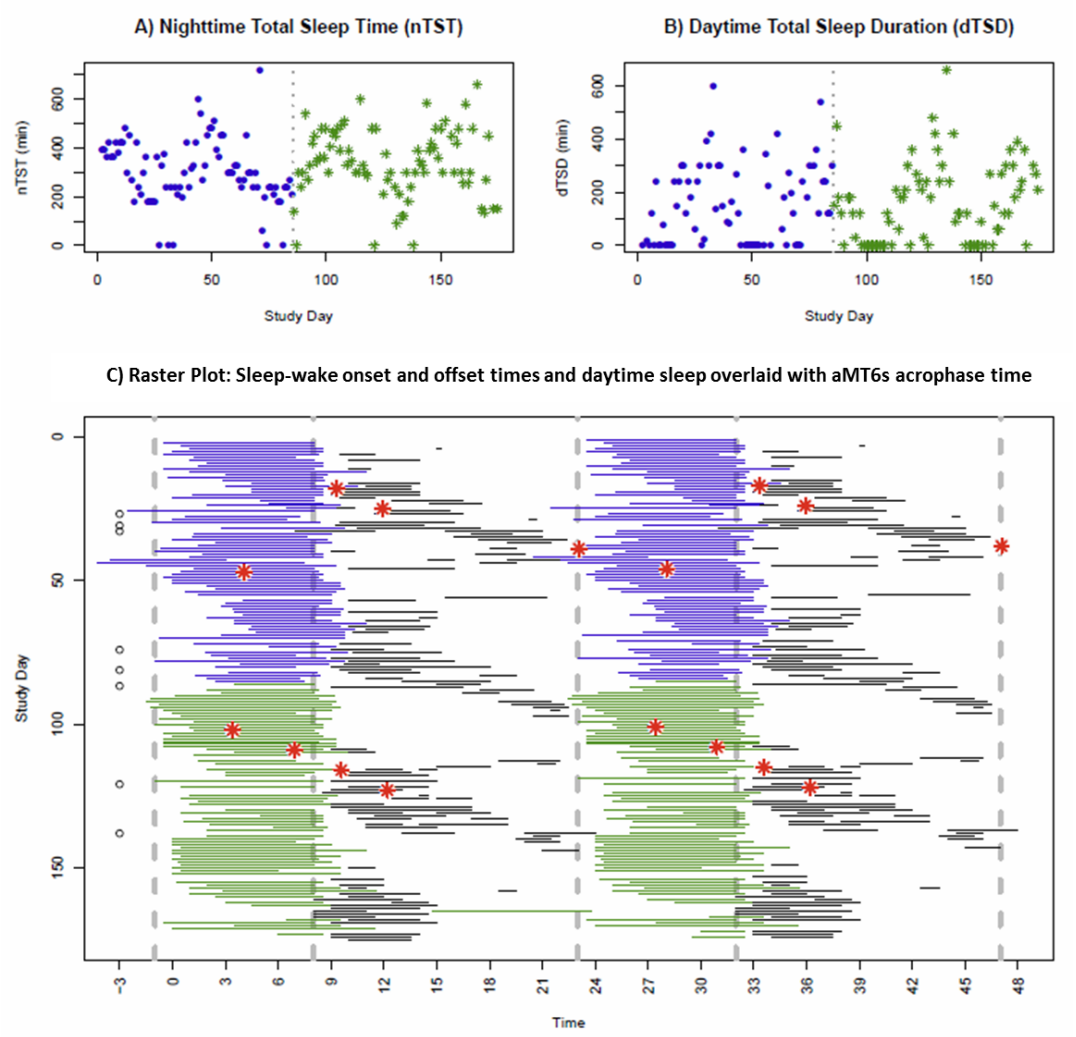


**Figure 25: Raster Plot of a Patient Whose Treatment Initiation Occurred Out-of-Phase**




The imprecision in predicting whether a patient will be in-phase or out-of-phase at a future time point (e.g. with the data collected in the SET study) makes the requested analysis un-informative. However, an analysis that can be performed that can provide insight into whether the treatment is corrective for the Non-24 cyclical pattern of the sleep-wake cycle is an analysis of the Absolute value of |Diff (in – out)|, as this would represent the change between phases regardless of assignment. Additionally, a sensitivity analysis can be performed by not using the absolute value but instead removing from the analysis population individuals with highly negative Diff (in-out) values, as they would suggest incorrect phase estimation.

### Analysis of Phase-Sleep Relationship (Absolute Value)

With the examination of the absolute value of change between phases regardless of phase assignment, the Placebo group should have a higher mean absolute value than the tasimelteon group if tasimelteon stabilizes the Non-24 cyclical pattern. The analysis

results and the number of subjects included in each analysis are shown in Table 30 and Table 31 for nTST and dTSD respectively.

**Table 30: Absolute Value of the Difference of nTST for In-Phase and Out-of-Phase**

| Cycle (N) | Placebo (Hour) | Tasimelteon (Hour) | Diff (Hour) | P-Value[1] | Permutation P-Value[2] |
|---|---|---|---|---|---|
| Cycle 1 (N= Placebo: 34; tasimelteon: 38) | 1.46 | 0.52 | 0.94 | 0.0006 | 0.0002 |
| Cycle 2 (N= Placebo: 32; tasimelteon: 37) | 1.03 | 0.52 | 0.52 | 0.0082 | 0.0078 |
| Cycle 1+2 (N= Placebo: 34; tasimelteon: 38) | 1.15 | 0.43 | 0.72 | 0.0007 | 0.0003 |

[1] P-value was based on analysis of variance model.
[2] P-value was based on the permutation ANOVA t-test

**Table 31: Absolute Value of the Difference of dTSD for In-phase and Out-of-phase**

| Cycle (N) | Placebo (Hour) | Tasimelteon (Hour) | Diff (Hour) | P-Value[1] | Permutation P-Value[2] |
|---|---|---|---|---|---|
| Cycle 1 (N= Placebo: 34; tasimelteon: 38) | 1.01 | 0.34 | 0.66 | 0.0070 | 0.0031 |
| Cycle 2 (N = Placebo: 32; tasimelteon: 37) | 0.66 | 0.26 | 0.40 | 0.0077 | 0.0065 |
| Cycle 1+2 (N= Placebo: 34;tasimelteon: 38) | 0.70 | 0.28 | 0.42 | 0.0211 | 0.0166 |

[1] P-value was based on analysis of variance model.
[2] P-value was based on the permutation ANOVA t-test

**Analysis of Phase-Sleep Relationship (Exclusion of Incorrect Phase)**

An additional analysis was performed in which subjects were removed from the Analysis population for whom Diff (in – out) was ≤ -0.75 hour in each cycle for nTST (or ≥ 0.75 for dTSD). For the analysis of the combined data (cycle 1+2), any subject removed in each individual cycle's analysis was also excluded. The analysis results, as well as the number of subjects included in the analysis are shown in Table 32 and Table 33 for nTST and dTSD respectively.

**Table 32: Difference of nTST Calculated for In-phase and Out-of-phase: Exclusion of Incorrect Phase**

| Cycle (N) | Placebo (Hour) | Tasimelteon (Hour) | Diff (Hour) | P-Value[1] | Permutation P-Value[2] |
|---|---|---|---|---|---|
| Cycle 1 (N= Placebo: 25; tasimelteon: 35) | 1.16 | 0.20 | 0.96 | 0.0029 | 0.0016 |
| Cycle 2 (N= Placebo: 23; tasimelteon: 35) | 0.71 | 0.16 | 0.55 | 0.0418 | 0.0483 |
| Cycle 1+2 (N= Placebo: 18; tasimelteon: 33) | 1.08 | 0.15 | 0.94 | 0.0035 | 0.0033 |

[1] P-value was based on the permutation ANOVA t-test
[2] P-value was based on the permutation ANOVA t-test

**Table 33: Difference of dTSD Calculated for In-phase and Out-of-phase: Exclusion of Incorrect Phase**

| Cycle (N) | Placebo (Hour) | Tasimelteon (Hour) | Diff (Hour) | P-Value[1] | Permutation P-Value[2] |
|---|---|---|---|---|---|
| Cycle 1 (N = Placebo: 31; tasimelteon: 33) | -0.84 | 0.07 | -0.91 | 0.0016 | 0.0006 |
| Cycle 2 (N = Placebo: 28; tasimelteon: 37) | -0.37 | -0.06 | -0.31 | 0.0392 | 0.0362 |
| Cycle 1+2 (N= Placebo: 28; tasimelteon: 33) | -0.66 | -0.01 | -0.65 | 0.0021 | 0.0013 |

[1] P-value was based on the permutation ANOVA t-test
[2] P-value was based on the permutation ANOVA t-test

The mean differences between the in-phase segment and out-of-phase segment was analyzed in the Analysis population by an ANOVA model with the fixed effect of pooled site and treatment group, as well as by a permutation ANOVA t-test. The permutation ANOVA t-test was conducted through the MULTTEST procedure in SAS on the residuals from the ANOVA model with only the pooled site adjusted.

In conclusion, both of these analyses support that tasimelteon is significantly more effective than placebo in reducing the variability of nTST and dTSD between in-phase and out-of-phase. In all of these analyses the tasimelteon group means are consistently closer to zero, representing a more stable sleep pattern.

## 6.5. Efficacy Summary

Tasimelteon 20 mg succeeded in the primary endpoint of entrainment of the melatonin rhythm as compared to placebo and in the primary endpoint of Clinical Response as measured by entrainment and the N24CRS in the SET Study.

Additionally, tasimelteon demonstrated significant entrainment of cortisol rhythms and clinically meaningful improvements across a number of patient reported outcomes including measures of total nighttime sleep, excessive day time sleep duration, and timing of sleep. Tasimelteon also showed significant improvements over placebo in clinician reported measures of global functioning as measured by CGI-C. These results provide robust evidence of a direct and clinically meaningful benefit to patients with Non-24.

In the RESET study tasimelteon demonstrated the maintenance effect of 20 mg of tasimelteon to entrain melatonin (primary endpoint) and cortisol circadian rhythms in individuals with Non-24. Tasimelteon treated patients maintained their clinical benefits while placebo treated patients showed significant deterioration in measures of nighttime sleep, excessive daytime sleep duration, and timing of sleep. The data from the SET and RESET studies demonstrate that tasimelteon is an effective treatment for Non-24-Hour Disorder in the totally blind.

# 7. TASIMELTEON SAFETY

## 7.1. Safety Analysis Populations

Safety data from the original NDA are provided below. This includes integrated and individual study safety data collected through the interim cut-off date of 30 November 2012. Adverse event (AE) data presented were coded using the Medical Dictionary for Regulatory Activities (MedDRA version 14.1). In order to maximize the safety data collected, safety analyses were conducted on multiple analysis populations. The primary population includes placebo-controlled data in Non-24. This is augmented by placebo-controlled data in other indications. Additionally, long-term analysis data is presented separately as placebo-controlled data is not available for the extended time period studied.

### 7.1.1. Primary Safety Analysis Population (Placebo-Controlled Non-24)

The primary safety analysis population provides the basis for the evaluation of the safety of tasimelteon in the target population. This includes integrated double-masked, placebo-controlled data from the SET and RESET studies.

### 7.1.2. Secondary Safety Analysis Population (Augmented Placebo-Controlled)

The secondary safety analysis population consists of the largest combined placebo controlled datasets from studies conducted in patients with Non-24 or insomnia. The purpose of this population is to broaden the scope of evaluation due to the quantitative limitations of the target population. The double-masked, placebo controlled phases of the SET study, 3204, and 004 are included in this population. Because of differences in study design, data from the Double-Masked Randomized-Withdrawal Phase of the RESET study is not included in this population.

### 7.1.3. Long-Term Safety Analysis Population (Non-24)

The long-term safety analysis population presents longitudinal safety data from all Non-24 subjects receiving tasimelteon in both placebo-controlled and open-label studies, or in combination of studies. Because of the rarity of Non-24 and low awareness among patients and healthcare providers, patients from the SET were enrolled in the RESET study as agreed upon with the FDA. Upon completion of either SET or RESET or both studies, subjects were provided the opportunity to enroll in to Study 3204, a long-term open-label safety study (Figure 4). This long-term analysis includes data from tasimelteon exposure only for subjects participating in SET, RESET, and/or 3204 as well as subjects participating in 3202 (a separate long-term open-label safety study).

## 7.2. Extent of Exposure

### 7.2.1. Exposure in all Tasimelteon Studies

As of 30 November 2012, more than 1,300 subjects have received at least one dose of tasimelteon in 22 separate clinical trials. Of these, 1,176 (87.4%) were exposed to at least one dose at or above the target level dose of 20 mg, with over half of these subjects exposed to the target dose level of 20 mg. See Table 34.

**Table 34: Summary of all (Unique) Subjects who received at least One Dose of Tasimelteon in all Clinical Trials**

| Study Phase | Study Population | <20 mg | 20 mg | > 20 mg | Any Dose |
|---|---|---|---|---|---|
| All | All subjects[1] | 170 | 621 | 555 | 1,346 |
| All Phase I Studies | All Phase I | 47 | 221 | 169 | 437 |
| | Healthy Subjects | 47 | 189 | 169 | 405 |
| | Hepatic Impairment | 0 | 16 | 0 | 16 |
| | Renal Impairment | 0 | 16 | 0 | 16 |
| All Phase II, III studies | All Phase II and Phase III | 123 | 400 | 386 | 909 |
| | Healthy subjects – Proof of concept of circadian regulation | 9 | 8 | 14 | 31 |
| | Healthy subjects – induced transient insomnia | 0 | 100 | 208 | 308 |
| | Insomnia/ primary insomnia | 114 | 109 | 164 | 387 |
| | Non-24-Hour disorder | 0 | 183 | 0 | 183 |

[1] Subjects exposed to more than one dose level in different treatment periods and/or in different studies are counted only once and are counted in the highest dose category

### 7.2.2. Exposure in Non-24-Hour Disorder

As of 30 November 2012, 183 patients with Non-24 received daily doses of tasimelteon for up 712 days. Of these, 111 (60.7%) were exposed for at least 6 months and 44 (24.0%) for at least 1 year. Total exposure was 46,116 person-days in Non-24.

As of 10 July 2013, at the time of the 120-day safety update cut-off, a total of 184 patients with Non-24 received daily doses of tasimelteon. Of these, 139 (75.5%) were exposed for at least 6 months, and 93 (50.5%) for at least 1 year. As of 10 July 2013, 107 patients with Non-24 continue to receive daily doses of tasimelteon in on-going safety studies.

### 7.2.3. Exposure in Safety Analysis Populations

Exposure within each of the safety analysis populations is presented in Table 35.

**Table 35: Safety Analysis Population Duration of Tasimelteon Exposure (days)**

| **Safety Analysis Population** | **Primary** | **Secondary** | **Long-term** |
|---|---|---|---|
| **Study Population** | **Non-24** | **Non-24 + Insomnia** | **Non-24** |
| **Dose** | **20 mg** | **1-50 mg** | **20 mg** |
| N | 52 | 429 | 183 |
| Mean (SD) | 143.3 (59.8) | 43.5 (42.7) | 252.0 (167.4) |
| Median | 182.0 | 34.0 | 243.0 |
| Range | 1 - 198 | 1 – 198 | 1 – 712 |

## 7.3. Safety Evaluations in Non-24 Clinical Studies

### 7.3.1. SET Study

In the pivotal Phase 3 study of tasimelteon (SET), 84 totally blind patients diagnosed with Non-24-Hour Disorder were randomized to receive either daily 20 mg tasimelteon therapy or placebo for 26 weeks.

#### 7.3.1.1. Safety Assessments in the SET Study

Safety assessments in the SET Study were performed at the screening, baseline, and all post-randomization study visits. Table 36 displays the schedule of assessments.

**Table 36: SET Study Schedule of Safety Assessments**

| Assessment | Screening Visit | Week 0 | Week 4 | Week 8 | Week 12 | Week 16 | Week 26 |
|---|---|---|---|---|---|---|---|
| Laboratory Assessments: Hematology, Chemistry, Urinalysis | X | X | X | X | X | X | X |
| Endocrine Testing | | X | X | X | X | X | X |
| Physical Exam | X | X | | | | | X |
| Vital Signs | X | X | X | X | X | X | X |
| Columbia Suicide Severity Rating Scale | X | X | X | X | X | X | X |
| Electrocardiogram | X | X | X | X | X | X | X |
| AE/SAE Collection | → | | | | | | |

### 7.3.2. RESET Study

In the Phase 3 randomized withdrawal study of tasimelteon (RESET), 20 totally blind patients diagnosed with Non-24-Hour Disorder were randomized to receive either daily 20 mg tasimelteon or placebo for 8 weeks following a 6-week open-label run-in period.

#### 7.3.2.1. Safety Assessments in the RESET Study

Safety Assessments in the RESET Study occurred throughout the Run-in and Randomized-Withdrawal Phases.

**Table 37: RESET Study Schedule of Safety Assessments**

| | Open-Label Tasimelteon Run-in | | | | Randomized Withdrawal | | |
|---|---|---|---|---|---|---|---|
| Assessment | Week 0 | Week 4 | Week 8 | Week 12 | Week 0 | Week 4 | Week 8 |
| Laboratory Assessments: Hematology, Chemistry, Urinalysis | X | X | X | X | X | X | X |
| Physical Exam | X | | | | X | | X |
| Vital Signs | X | X | X | X | X | X | X |
| Columbia Suicide Severity Rating Scale | X | X | X | X | X | X | X |
| Electrocardiogram | X | X | X | X | X | X | X |
| AE/SAE Collection | → | | | | | | |

## 7.4. Tasimelteon Integrated Safety Data

Safety data is presented for the primary safety analysis and is augmented by the secondary safety analysis and the long-term safety analysis.

### 7.4.1. Deaths and Serious Adverse Events

There were no deaths in the tasimelteon clinical development program.

A serious adverse event (SAE) is any untoward medical occurrence in a subject administered a medicinal product at any dose that results in death, is life-threatening, requires inpatient hospitalization or prolongation of hospitalization, results in persistent or significant disability/incapacity, or results in a congenial anomaly/birth defect. Other events determined to be important, based on medical judgment, may be reported as an important medical event (IME). The term “treatment-emergent” adverse event (TEAE) refers to an AE that occurred or worsened on or after the first dose of tasimelteon or placebo.

In placebo-controlled studies, SAEs were reported in 7/429 (1.6%) of tasimelteon-treated subjects and in 3/203 (1.5%) placebo-treated subjects. All events were unrelated to tasimelteon.

Table 38 lists patients who had an SAE during the Randomization Phase of the study. Of the 84 treated patients, 2 patients in the tasimelteon group had a treatment-emergent SAE and 4 patients (2 in each treatment group) had SAEs that began before or after the treatment period and therefore were not considered to be treatment emergent. None of the SAEs resulted in study discontinuation.

**Table 38: Serious Adverse Events occurring in the SET Study**

| Treatment Patient No. | Adverse Event Description | TEAE | Severity | Relationship to Study Drug | Resulted in Discontinuation |
|---|---|---|---|---|---|
| **Placebo** | | | | | |
| Patient [redacted] | Procedural pain | No[1] | Severe | Unrelated | No |
| Patient [redacted] | Small intestinal obstruction prior to treatment initiation [redacted] with history of intestinal obstruction | No | Severe | Unrelated | No |
| **Tasimelteon 20 mg** | | | | | |
| Patient [redacted] | Syncope during blood draw [redacted]. Treatment continued after 2 day interruption. | Yes | Severe | Unrelated | No |
| Patient [redacted] | Acute lymphocytic leukaemiadiagnosed [redacted] | No | Severe | Unrelated | No[2] |
| Patient [redacted] | Cholecystitis [redacted] prior to treatment initiation. Patient was treated with tasimelteon after resolution. | No | Severe | Unrelated | No |
| Patient [redacted] | Diverticulitis[3] | Yes | Moderate | Unrelated | No |

TEAE = treatment-emergent adverse event.
[1] Event not considered treatment emergent in the SET study as onset date was during the RESET study.
[2] Patient discontinued due to event of syncope which was likely related to the SAE of ALL
[3] On 26JUL12, the investigator updated the event classification to Non-serious Important Medical Event.

Table 39 lists patients who had an SAE during the RESET study. Of the 57 patients treated during the Run-in Phase, 2 patients in the tasimelteon group had a treatment-emergent SAE and one of these SAEs resulted in study discontinuation. In addition, one

patient had a pre-treatment SAE. There were no SAEs during the Randomized Withdrawal Phase.

**Table 39: Serious Adverse Events occurring in the RESET Study**

| Treatment Patient No. | Adverse Event Preferred Term | TEAE | Severity | Relationship to Study drug | Resulted in Discontinuation |
|---|---|---|---|---|---|
| **Pre-treatment** | | | | | |
| Patient [redacted] | Serotonin syndrome | No | Moderate | Unrelated | No |
| **Tasimelteon 20 mg** | | | | | |
| Patient [redacted] | Procedural pain | Yes | Severe | Unrelated | No |
| Patient [redacted] | Loss of consciousness | Yes | Severe | Unrelated | Yes |

TEAE = treatment-emergent adverse event.

Two (2) patients had a treatment-emergent SAE during the Open-Label Phase of the SET study. Neither of the SAEs resulted in study discontinuation. Of the 86 patients who received tasimelteon in Study 3204, 3 (3.5%) patients had a treatment-emergent SAE. No specific SAE preferred term was reported more than once and none of the SAEs resulted in study discontinuation. There were no SAEs in Study 3202.

### Adverse Events

### Common Adverse Events in the Primary Safety Analysis

The most frequently occurring AEs in the primary safety analysis are listed in Table 40.

**Table 40: Adverse Events by Preferred Term – Primary Safety Analysis**

| Preferred Term | Tasimelteon 20 mg (N=52) | Placebo (N=52) |
|---|---|---|
| Headache | 8 (15.4%) | 3 (5.8%) |
| Alanine aminotransferase increased | 5 (9.6%) | 2 (3.8%) |
| Vivid or Unusual Dreams[a] | 4 (7.7%) | 0 |
| Somnolence | 3 (5.8%) | 1 (1.9%) |
| Upper Respiratory tract infection | 3 (5.8%) | 0 |
| Urinary tract infection | 3 (5.8%) | 1 (1.9%) |
| Conduction disorder | 3 (5.8%) | 0 |
| Sleep disorder | 3 (5.8%) | 0 |

[a] Includes multiple preferred terms: abnormal dreams, nightmare.
Events occurring in at least 5% of tasimelteon group and in at least 2X frequency of placebo group are presented

**Common Adverse Events in the Secondary Safety Analysis**

The most frequently reported AEs in the Secondary Safety Analysis were headache, nasopharyngitis and somnolence. (Table 41) Of these, only headache occurred at a significantly higher rate in the tasimelteon group when compared to the placebo group. No other events occurred at a rate ≥ 3% in the tasimelteon group.

**Table 41: Adverse Events, Preferred Terms ≥ 3% in the Secondary Safety Analysis**

| Preferred Term | All Tasimelteon (N=429) | Placebo (N=203) |
|---|---|---|
| Headache | 41 (9.6%) | 15 (7.4%) |
| Nasopharyngitis | 28 (6.5%) | 13 (6.4%) |
| Somnolence | 13 (3.0%) | 3 (1.5%) |

TEAEs were reported as severe in 5.1% of tasimelteon-treated subjects, as compared to a clinically similar rate of 6.4% in the placebo group. Only 3 TEAEs were assessed by investigators to be severe in more than 1 instance in tasimelteon-treated subjects: nasopharyngitis, vivid or unusual dreams, and syncope. TEAEs assessed to be drug-related were reported in 23.8% of subjects in the tasimelteon group, with a similar rate of 17.7% reported in the placebo group. Among these, only headache was reported at a rate ≥ 3% among tasimelteon-treated patients, although the rate (5.8%) was clinically similar to the rate in placebo-treated patients (4.4%).

**Common Adverse Events in the Long-term Safety Analysis**

The most frequently reported AEs (occurring in ≥ 5.0% of subjects) in the long-term safety analysis population were headache, nasopharyngitis, urinary tract infection, alanine aminotransferase increased, and vivid or unusual dreams.

**Adverse Events Leading to Discontinuations**

In all subjects in all studies, 32/1346 (2.4%) tasimelteon-treated subjects and 7/306 (2.3%) placebo treated subjects permanently discontinued study medication due to an adverse event.

**Adverse Events Leading to Discontinuation in the Primary Safety Analysis**

In the primary safety analysis (SET and RESET studies), 3/52 (5.7%) tasimelteon-treated patients and 2/52 (3.8%) of placebo-treated patients had study treatment permanently discontinued due to a TEAE. One additional patient (Patient [redacted]) was discontinued due to an AE that began prior to study treatment and therefore was not considered treatment-emergent. None of the AEs that led to study discontinuation were considered serious and no specific AE preferred term that led to study discontinuation was reported

more than once. In the SET study, Patient [redacted] discontinued due to the event of syncope which was likely related to ALL (reported as an SAE). There were no discontinuations during the randomized withdrawal phase of the RESET study.

**Adverse Events Leading to Discontinuation in the Secondary Safety Analysis**

In the secondary safety analysis, 14/429 (3.3%) tasimelteon-treated patients and 6/203 (3.0%) placebo-treated patients permanently discontinued study drug due to a treatment-emergent adverse event.

**Adverse Drug Reactions**

A summary of adverse drug reactions can be found in Table 42.

**Table 42: Adverse Drug Reactions in Placebo-Controlled Studies of Tasimelteon**

| | Primary Safety Analysis | | Secondary Safety Analysis | |
|---|---|---|---|---|
| **Preferred Term** | **Non-24 Placebo (N=52)** | **Non-24 Tasimelteon 20 mg (N=52)** | **Placebo (N=203)** | **Tasimelteon 1-50 mg (N=429)** |
| Headache | 3 (5.8%) | 8 (15.4%) | 15 (7.4%) | 41 (9.6%) |
| Vivid or Unusual Dreams[a] | 0 | 4 (7.7%) | 1 (0.5%) | 11 (2.6%) |

[a] includes multiple preferred terms: abnormal dreams; nightmare

## 7.5. Safety Topics of Special Interest

### 7.5.1. Laboratory Values and Vital Signs

No clinically significant differences in laboratory values or vital sign changes were found within the clinical safety database for tasimelteon.

In the Common Adverse Events in the Long-term Safety Analysis Section above alanine aminotransferase increase was reported as occurring in ≥ 5.0% of the subjects. None of the alanine aminotransferase (ALT) elevations were considered clinically notable by the respective site PI. No subject had an ALT elevation suggestive of Drug-Induced Liver Injury (DILI), and only two subjects had an ALT elevation ≥ 5x ULN, one whose ALT levels remained consistent with ALT levels measured at baseline, and one who experienced a transient elevation that resolved spontaneously 12 days later and did not recur. Neither subject experienced symptoms of hepatic dysfunction. There is no clinically meaningful evidence for DILI risk associated with tasimelteon treatment.

### 7.5.2. Endocrine (SET Study)

Under the efficacy section we discussed the beneficial effects of tasimelteon in the regulation of the circadian rhythms of melatonin and cortisol. We have also performed a number of safety assessments of endocrine laboratory parameters with standard methods.

Evaluation of reported endocrine- and metabolic-related adverse events was undertaken in the SET study per FDA recommendation. All events coding to the SOCs of Endocrine Disorders, all endocrine-related events coded to Metabolic and Nutrition Disorders, and all events coding to Investigations that were endocrine-related, were compiled and analyzed in order to identify a safety trend or signal for adverse endocrine effects. Endocrine parameters assessed in the SET study included serum total thyroxine (T4), free T4, thyroid stimulating hormone (TSH), triiodothyronine (T3) , fasting ACTH stimulation test, cortisol, total testosterone, free testosterone, luteinizing hormone (LH) , follicle stimulating hormone (FSH), progesterone, and prolactin.

The rate of endocrine and endocrine-related events was similar in tasimelteon-treated subjects compared to placebo among Non-24 subjects in the SET study. There was no impact on safety and no associated reported clinical adverse events. There were no clinically meaningful or persistent changes from baseline at any time point for any endocrine laboratory parameter. In both the tasimelteon and placebo groups, the majority of subjects had normal endocrine parameter values at baseline and post-baseline. Among shifts from baseline to worst value post-baseline, the most commonly observed differences between tasimelteon and placebo groups were normal to low shifts in prolactin (15.4% of tasimelteon subjects vs. 5.6% of placebo subjects), and total testosterone (13.6% of tasimelteon subjects vs. 19.0% of placebo subjects), and normal to high shifts in luteinizing hormone (4.5% of tasimelteon subjects vs. 19.0% of placebo subjects), and thyroid stimulating hormone (10.3% of tasimelteon subjects vs. 16.7% of placebo subjects). All of these changes were transient and not considered clinically relevant. Given these results, there is no evidence of any adverse effect on laboratory measures of endocrine function due to tasimelteon use.

### 7.5.3. Next-Day Effects

The potential of next day residual effects of tasimelteon on function and somnolence was investigated during clinical development. Study 1108 was performed to measure the cognitive effects of tasimelteon on subjects over a 24-hour period following receipt of a single 20 mg oral dose of tasimelteon, both alone and in conjunction with alcohol. The results of this study showed that, although there are some minor effects on attention and cognition in the first 3 hours post-dose with tasimelteon alone, values returned to baseline levels by 8 hours post-dose. Administration of tasimelteon alone did not have any

significant effects on any subjective or objective measures of sustained attention, cognition, balance, or psychomotor function.

Subsequently, next day residual effect was reviewed across multiple studies. Study 001 tested the Digit Symbol Substitution Test (DSST) and Study 2101 assessed the Psychomotor Vigilance Test throughout the day while Studies 3101 and 3104 tested DSST and Visual Analog Scale (VAS) approximately 1 hour after awakening. No notable differences in cognitive performance or mood were observed in subjects receiving tasimelteon when compared with subjects receiving placebo. Study 004 did not specifically assess residual effects but the Weekly Sleep Questionnaire (WSQ) included questions about how the subject felt upon awakening. The analysis of this questionnaire showed that changes during treatment were generally small, and no significant differences were observed between the placebo and tasimelteon treatment groups. In Study 2101, a Psychomotor Vigilance Test did not detect differences between baseline and post-treatment test when assessed throughout the day including the morning, though the study was underpowered for this purpose. In Study 3101, the DSST was administered on Day 1 (baseline) and post-treatment approximately 1 hour after being awakened on Day 2. Based on analysis of the results obtained, tasimelteon was found to have no significant effect on the change from baseline to post-treatment values in cognitive performance relative to placebo. In Study 3104, both the DSST and the VAS were utilized, and numerically greater improvements in subjective daytime function were observed for subjects receiving 20 mg tasimelteon when compared with subjects receiving placebo.

Based on these findings, no evidence of daytime somnolence, sleepiness or other "next-day effects" was expected during clinical studies of tasimelteon use as indicated (i.e. 20 mg taken orally 1 hour prior to bedtime at the same time each night). In fact, the differences in somnolence rates between tasimelteon-treated Non-24 subjects and placebo subjects throughout clinical development in general were not clinically meaningful. Analysis of the timing of first episode of somnolence events in the primary safety analysis revealed no additional information. Thus, based upon all of the available evidence, residual daytime effects resulting from tasimelteon use are unlikely with the recommended dose of 20 mg once per day one hour prior to bedtime, and it is reasonable to conclude that somnolence events are rare and not a safety signal.

### 7.5.4. Vivid or Unusual Dreams

Vivid dreams are seen in a small percentage of patients treated with tasimelteon. Due to the subjective nature of dream reporting (by both subject and Investigator), reported events that code (per MedDRA 14.1) to the preferred terms of abnormal dreams and nightmare were aggregated into a common event term hereafter referred to as, "vivid or unusual dreams" in order to better ascertain the incidence, timing, and overall prevalence of these events during the course of tasimelteon treatment. These events were reported at

a low rate, but exclusively among tasimelteon-treated subjects in the primary safety analysis, and at a higher rate among tasimelteon-treated subjects compared to placebo subjects in the expanded secondary safety analysis of all placebo-controlled efficacy studies.

Examination of first event of "vivid or unusual dreams" among tasimelteon-treated subjects in the primary and expanded safety analyses revealed that these events were largely transient and mild in nature without sequelae, and could be reported at any time after initiation of treatment. While the mechanism of this effect is not fully known, it is likely related to the mechanism of action of tasimelteon and its effect to normalize REM stage sleep accumulation, with more REM episodes occurring during the later stages of a sleep episode (17). Such patients, especially those with prolonged disruption of sleep patterns such as Non-24 patients, are more likely to both enter sleep and wake up in close temporal proximity to a REM episode, and are therefore more likely to remember and report their dream content. Importantly, none of these events were associated with disruptive sleep behaviors, or of a duration sufficiently long enough, to be characterized as parasomnias, either by Investigators or per ICSD guidelines (29).

### 7.5.5. Potential for Suicidality

Subjects in Studies SET, 3202, RESET, 3204 and phase I studies 1106, 1108, 1111, and 1112 were required to complete the Columbia Suicide Severity Rating Scale (C-SSRS) at screening, baseline, and subsequent study visits. Results of these interviews were compiled to determine if there was any clinically or statistically meaningful impact on subject-reported suicidal ideations or behaviors during the course of the clinical studies. In the primary safety analysis, 4 subjects (3 in the placebo group, 1 in the tasimelteon group), had any suicidal ideation during the clinical studies. No subjects in either the tasimelteon or placebo group had suicidal behavior during the studies. These results suggest that there is no evidence of risk due to suicidal ideations or behavior associated with tasimelteon 20 mg.

### 7.5.6. Assessment of Potential for Withdrawal and Abuse

To date, a questionnaire specific to circadian regulators has not been developed and consequently the Tyrer Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) was deemed to be the most appropriate tool and thus was administered in Studies 3104, SET and RESET.

In 196 tasimelteon-treated subjects from Study 3104 the abrupt discontinuation of 20 and 50 mg tasimelteon after 5 weeks of treatment did not appear to cause the types of subjective withdrawal symptoms experienced with benzodiazepines in pharmacologically dependent subjects as measured by BWSQ taken one day after discontinuation. In the SET Study, the BWSQ was completed during the 2-week placebo wash-out period

following 6 months of treatment. In RESET, the BWSQ was completed after at least 3 months of open-label tasimelteon treatment during the randomized withdrawal phase. The questionnaire was administered to 11 subjects in SET and 20 subjects in RESET. No differences were observed between treatment groups in either study. Likewise, no withdrawal symptoms were seen during a one week washout period following abrupt discontinuation of a 4 week double-blind treatment phase in 149 subjects treated with 1-, 10-, and 50 mg tasimelteon as measured by adverse events, safety labs, physical and a Profile of Mood States questionnaire (CN116-004). Based upon all of the available data, there is no evidence of withdrawal or abuse associated with tasimelteon use.

## 7.6. Safety Conclusions

Tasimelteon is well-tolerated in the indicated population of totally blind individuals with Non-24-Hour Disorder, and the safety profile of tasimelteon is favorable. In both the SET pivotal efficacy study and the RESET randomized withdrawal study, events reported among tasimelteon-treated patients were of similar type, severity, and frequency compared to events occurring in placebo-treated patients. Among all tasimelteon-treated patients in placebo-controlled Phase 2 and 3 efficacy studies, there were no serious adverse events that were assessed to be related to tasimelteon treatment. Additionally, no clinically relevant events, trends, or changes were identified in clinical or laboratory endocrine parameters in the SET study. Throughout the clinical development program, the most common adverse reactions occurring at a level clinically different from placebo are headache and vivid or unusual dreams. In summary, tasimelteon has been demonstrated during clinical studies to be well-tolerated with a favorable safety profile.

# 8. BENEFIT-RISK CONSIDERATIONS

The benefits of tasimelteon in the treatment of totally blind patients with this serious and orphan Non-24-Hour Disorder have been established in two pivotal clinical studies. Specifically, tasimelteon was shown to entrain (synchronize) the Master clock to a 24-hour period, as measured by both the melatonin and cortisol circadian rhythm measurements. More than fifty percent of patients that received tasimelteon treatment for an adequate duration (approximately one circadian cycle length or 40 to 80 days) were successfully entrained. In addition tasimelteon was shown to restore the 24-hour synchrony of the sleep-wake cycle. As a result, tasimelteon significantly and meaningfully improved the timing and amount of sleep episodes, allowing sleep to be consolidated during the night and sleep during the day to be minimized. Entrainment and improvements in the sleep-wake cycle are maintained when tasimelteon treatment is taken at the same time every night. Physician derived global functioning impression showed consistent improvements in the overall function and well-being of tasimelteon-treated study participants. Tasimelteon was also shown to be well tolerated with a mild side effect profile compatible with chronic use.

Tasimelteon, if approved, will become the first pharmacological treatment for Non-24 in more than 60 years since this serious and distressing disorder was first described. Given the combination of specific and meaningful effects coupled with a good tolerability profile demonstrate that the overall benefit- risk ratio of tasimelteon, a circadian regulator for the treatment of Non-24 in the totally blind, is favorable.

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# 10. APPENDIX A – LISTING OF TASIMELTEON CLINICAL STUDIES

**Table 43: Listing of Clinical Studies Conducted for the Development of Tasimelteon**

| Study ID | Type of Study | Dosage | N | Duration of Treatment |
|---|---|---|---|---|
| CN116-001 | Dose escalation study in HV | tasimelteon 1-300 mg<br>PBO | 48 | Single dose PBO lead-in followed by single dose |
| CN116-002 | Dose escalation study in HV | tasimelteon 1-150 mg<br>PBO | 32 | Single dose PBO lead-in followed by 28 days |
| CN116-003 | Safety, PK and PD in young and elderly HV | tasimelteon 50 mg<br>PBO | 40 | Single doses, separated by 7 day wash-out |
| CN116-004 | Efficacy and safety in elderly subjects with primary insomnia | tasimelteon 1- 50 mg<br>PBO | 227 | 28 days followed by 1 week placebo |
| CN116-005 | Efficacy in young night shift workers | tasimelteon 1 -50 mg<br>PBO | 3 | Single doses, separated by at least 7 day wash-out |
| VP-VEC-162-1101 | AME in males HV | tasimelteon<br>100 mg (100 µCi) [$^{14}$C]-tasimelteon solution | 6 | Single dose |
| VP-VEC-162-1102 | Food effect in HV | tasimelteon 100 mg | 26 | 2 single doses (1 Fasted; 1 Fed), separated by 7 day wash-out |
| VP-VEC-162-1103 | Thorough QT in HV | tasimelteon 20 and 300 mg<br>moxifloxacin 400 mg<br>PBO | 44 | 3 days followed by 4 day wash-out |
| VP-VEC-162-1104 | DDI with midazolam in HV | tasimelteon 100 mg<br>midazolam 10 mg | 24 | 7 days tasimelteon, 2 single doses midazolam |
| VP-VEC-162-1105 | Effect of hepatic impairment on PK | tasimelteon 20 mg | 29 | Single dose |

| Study ID | Type of Study | Dosage | N | Duration of Treatment |
|---|---|---|---|---|
| VP-VEC-162-1106 | Effect of renal impairment on PK | tasimelteon 20 mg | 32 | Single dose |
| VP-VEC-162-1107 | Effects of intrinsic factors and smoking status on PK of young HV and Elderly non-smokers | tasimelteon 20 mg | 60 | Single dose |
| VP-VEC-162-1108 | PK and PD interactions with ethanol in HV | tasimelteon 20 mg<br>ethanol 0.6 g/kg (female) or 0.7 g/kg (male)<br>PBO | 28 | Single doses of tasimelteon and ethanol in combination with each other and placebo |
| VP-VEC-162-1110 | DDI to assess impact on CYP450 3A4 and 2C8 in HV | tasimelteon 20 mg<br>midazolam 10 mg<br>rosiglitazone 4 mg | 24 | 16 days tasimelteon, 2 single doses of midazolam and rosiglitazone |
| VP-VEC-162-1111 | DDI to assess impact of combination treatment of a CYP1A2 inhibitor on PK parameters | tasimelteon 5 mg<br>fluvoxamine 50 mg | 24 | 2 single doses tasimelteon, 7 days fluvoxamine |
| VP-VEC-162-1112 | DDI to assess impact of combination treatment of a CYP3A4 inhibitor and CYP3A4 inducer on PK parameters | tasimelteon 20 mg<br>ketoconazole 400 mg or<br>rifampin 600 mg | 48 | 2 single doses tasimelteon, 5 days ketoconazole or 10 days rifampin |
| VP-VEC-162-2101 | 5 hour phase advance POC study in HV | tasimelteon 10 – 100 mg<br>PBO | 39 | 3 days |
| VP-VEC-162-3101 | Efficacy and safety study in HV with induced transient insomnia | tasimelteon 20 - 100 mg<br>PBO | 412 | Single dose |
| VP-VEC-162-3104 | Efficacy and safety study in subjects with primary insomnia | tasimelteon 20- 50 mg<br>PBO | 322 | 35 days |

| Study ID | Type of Study | Dosage | N | Duration of Treatment |
|---|---|---|---|---|
| VP-VEC-162-3201 | Efficacy and safety study in totally blind subjects with Non-24 | tasimelteon 20 mg<br>PBO | SET: 84<br>OLE: 51 | 26 weeks randomized; 26 weeks open-label |
| VP-VEC-162-3202 | Long-term OL safety study in totally blind subjects with Non-24 | tasimelteon 20 mg | 140 planned | 52 weeks followed by a 3 year optional sub-study |
| VP-VEC-162-3203 | Randomized withdrawal study in totally blind subjects with Non-24 | tasimelteon 20 mg<br>PBO | 20 | 20-24 weeks |
| VP-VEC-162-3204 | Long-term OL safety study in totally blind subjects with Non-24 | tasimelteon 20 mg | 200 planned | 2 years |